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THE MEDICAL TREATMENT OF THE THYROCARDIAC.*

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The Graduate Fortnight of the New York Academy of Medicine, so recently terminated, has dealt rather extensively with hyperthyroidism, hence I need not burden you with a repetition of the general clinical picture of the thyrotoxic state. Nor does there seem to be need to discuss in detail the diagnosis of thyrotoxicosis or the clinical differentiation between the hyperthyroidism of Graves' disease and that present in toxic nodular goiter, if, indeed, there be any. The factor of first importance in the thyrocardiac is the presence of thyrotoxicosis, and this is common to both clinical forms of the disease. What is meant by the term "Thyrocardiac?" Perhaps as satisfactory a definition as any is: The thyrocardiac patient is one who presents the combination of hyperthyroidism with evidences of cardiac failure, either congestive or anginal, with or without evidence of structural lesions in the heart or arteries.

The incidence of thyrocardiac trouble as determined statistically varies widely in different parts of the world, in different clinics in the same country, in the different age groups and somewhat according to whether one is dealing with Graves' disease or with the toxic form of nodular goiter. It is probably both useless and misleading, therefore, to attempt any numerical statement of incidence but it may safely be said that the condition is decidedly commoner than is generally recognized.

That the structurally normal heart is subjected to overwork in hyperthyroidism is evidenced by the almost constant tachycardia

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which persists with little diminution during sleep. It is even present in the isolated, perfused heart from the animal poisoned by thyroxin or thyroid extract and has been observed in surviving, isolated segments of such poisoned hearts. It is therefore due, in part at least, to a direct poisoning of the heart muscle itself. Such a poisoned heart has been shown, also, to exhibit increased oxygen consumption, an increased lactic acid production and a hypersensitiveness to relative oxygen want; all of which indicate the presence of a fundamental change causing increased rate of myocardial metabolism.

Despite the evidence of pronounced poisoning of the myocardium, postmortem studies fail to show any constant structural changes other than hypertrophy. Occasional instances of toxic inflammatory myocarditis have been found without other discoverable cause than the thyroid intoxication. The common absence of structural change is quite in harmony with the clinical observation that ablation of the thyroid gland is often followed by prompt and lasting disappearance of all evidences of heart impairment in cases previously suffering from marked congestive failure and auricular fibrillation. Finally structural changes are not found in the hearts of animals poisoned by thyroid or thyroxin. It is evident that the toxic effects upon the heart are for the most part functional and reversible.

In view of the elevated general basal metabolism of hyperthyroidism, it is not surprising to find such other common manifestations of cardiac overwork as: hypertrophy of the heart; visible and palpable cardiac overactivity; increased blood pressure; dyspnea on mild exertion; and marked fatigability. Furthermore, disturbances of rhythm are frequent, especially auricular fibrillation and sometimes flutter, less often heart-block and extrasystoles. All of these are probably due to direct cardiac intoxication and heightened sympathetic activity. When present, they impose an added load upon the heart and systemic circulation.

It is not, therefore, a cause of wonder that cardiac failure sometimes complicates hyperthyroidism in patients otherwise free from cardiac or vascular disease. It is remarkable rather under such circumstances that failure of the otherwise sound heart is relatively uncommon. The majority of patients classifiable as thyrocardiac are found among those in whom there are present both hyperthyroidism and structural cardiac or vascular disease. In these the load imposed by the thyrotoxicosis is the factor primarily responsible for the development of the manifestations of cardiac failure.

Four clinical groups of thyrocardiac patients may be distinguished: First are those under 40 in whom the cardiac failure is apparently due entirely to the toxic effects of Graves' disease. The diagnosis of Graves' disease is usually evident from its well developed symptoms. Cardiac failure is of the congestive type and is rarely very pronounced. The cardiac overaction with its attendant tachycardia, sharp and accentuated apical first sound, apical systolic murmur, accentuated pulmonic second sound, the occasional accentuation

of the third heart sound, frequent auricular fibrillation, and evidences of pulmonary congestion may lead to the suspicion that mitral stenosis is present. It is not always possible to be sure whether or not it is present as a complicating factor in a given case. It is likely that the phenomena are merely due to a greatly overacting, structurally intact heart if they have developed more or less simultaneously with the symptoms of the hyperthyroidism and if close investigation of the patient's past history fails to reveal frequent tonsillitis, chorea, or evidences of rheumatism. The disappearance of the phenomena with the removal of the thyrotoxicosis gives the final answer.

The second group differs from the first only in the knowledge of a pre-existing rheumatic cardiac damage. This group is usually recognized easily by the history and is confirmed by the rather poor response to the usual régime of treatment of the rheumatic cardiac, especially to the use of digitalis.

The third group comprises patients of more than 45 in whom the cardiac phenomena may be due in part to syphilitic, hypertensive or arteriosclerotic changes in the heart. While such structural cardiac changes are often contributory, the cardiac failure is generally precipitated and often maintained by the thyrotoxic state. The underlying cardiac damage may or may not be recognized. The heart failure in this group is usually of the congestive type, though the picture may be that of angina pectoris.

Finally, the fourth group is that of "Masked hyperthyroidism." Here the patients are generally also over 45 and show clinical signs and symptoms predominantly cardiac. Those of hyperthyroidism may be almost wholly wanting. Suspicion of thyrotoxicosis is often raised because of poor response to cardiac therapy, because of the disproportion between the degree of heart failure and the manifest evidences of organic cardiovascular disease, or by both. Diagnosis is established by determinations of the basal metabolism, which, however, may be but slightly elevated; by the findings of slight signs of hyperthyroidism and nodules in the thyroid; or by a therapeutic test with iodin controlled by repeated measurements of the metabolism.

Graves' disease, as mentioned, is the common thyroid disturbance in the first two groups while either Graves' or the toxic form of adenoma may be present in the latter two. Toxic adenoma is probably the commoner in the fourth group.

Differentiation of these groups, while generally possible, is of relatively minor importance so far as immediate treatment is concerned. Their recognition does, however, alter the prospect of later treatment and is of material signficance in the matter of ultimate prognosis, especially as to the probability of recurrence of heart failure.

The treatment of the thyrocardiac patient presents two problems: 1. The cardiac failure. 2. The hyperthyroidism. It is a

mistake, however, even where organic heart disease is present in marked degree, to lose sight of the all-important hyperthyroidism. Experience has amply proved that relatively little and sometimes no satisfactory restoration of the heart can be secured so long as the thyrotoxicosis exists. The administration of digitalis rarely controls the heart failure adequately in thyrocardiac patients exhibiting a regular sinus rhythm and is scarcely more effective in those whose hearts show auricular fibrillation. The thyroid toxins seem to be altogether too potent to have their cardiac actions significantly offset by even so powerful a cardiac drug as digitalis. Quinidin will restore the sinus rhythm in many of these patients, but usually the cardiac failure will still persist. This is not to say that these agents are of no value in the care of the thyrocardiac. They often are of help, but the benefits derived from their use are relatively slight and restoration of full cardiac efficiency is seldom attained by their use alone. Treatment must always be directed toward the control of the hyperthyroidism, the cardiac phenomena being dealt with as complications which may or may not be eliminated by control of the thyrotoxicosis.

There are two schools of thought concerning the treatment of hyperthyroidism—the medical and the surgical. My personal leanings used to be toward the medical a number of years ago, especially for the thyrocardiac patient who too often succumbed promptly to operative manipulations on and about his thyroid gland. Medical treatment, if adequately and painstakingly conducted over a sufficiently long period, was capable of curing some cases of Graves' disease and of restoring many others to a reasonable state of health. But at best the results were problematic and failure was the rule in the thyrocardiac case, death merely being deferred for months of progressively increasing invalidism. The results in the thyrocardiac with toxic adenoma were still less promising under medical management. The patient in whom the clinical picture was predominantly cardiac, that is the patient with masked hyperthyroidism, offered an almost hopeless prognosis, probably because the presence of thyrotoxicosis was seldom recognized.

Within the past 10 years, and even more within the past few, both our knowledge of hyperthyroidism and of its combined medical and surgical treatment and our ability to recognize and to treat the thyrocardiac have been advanced enormously by the joint labors of internists and surgeons. Today the proper admixture of medical and surgical therapy makes the results of treatment of the thyrocardiac often so brilliant as to be among our most dramatic therapeutic accomplishments. The outstanding fact today is that these patients can and must be relieved of their thyrotoxicosis through subtotal thyroidectomy. I believe that surgery is an essential step in their successful care and that the prognosis has been changed from generally very bad to generally very favorable, and often to most excellent. This reversal of outlook depends upon the fulfil-

ment of two, and sometimes three groups of requirements. Two of these are medical and one surgical. I shall leave the latter to Dr. Parsons, reserving the privilege of emphasizing a few points that are at least as much medical as surgical. The first requirement is that of pre-operative medical treatment, to have the patient in the most favorable condition to withstand both the operation itself and the immediate postoperative risks.

Before beginning pre-operative treatment the surgeon should be asked to examine the patient so that he may then determine the wisest surgical program on the basis of the patient's condition when at its worst. He will then not be misled into adopting procedures more radical than the patient might safely be expected to withstand. The importance of this step has just been emphasized by Lahey during the Academy Fortnight.

Physical and mental rest are among the first desiderata in pre-operative medical treatment. The patient should be confined to bed in quiet surroundings and given sufficient sedatives to control his nervousness. The bromids, alone or with hydrated chloral, or the barbiturates such as phenobarbital, amytal, etc., are generally the most satisfactory. The dose should be repeated 3 or 4 times daily and should be just sufficient to produce definite but mild sedation in the given patient. The actual amount will vary rather widely in different patients. It is seldom necessary to resort to the opiates and their use should generally be restricted to the alleviation of severe dyspnea and its attendant mental distress in the first few days of treatment. For this purpose morphin is the agent of choice, and it should be administered hypodermically. The dose should be from 10 to 20 mg. (gr. $\frac{1}{6}$ to gr. $\frac{1}{3}$). Scopolamin, with or without morphin, has been recommended, but I do not favor it because its actions are untrustworthy, it has a pronounced tendency to cause delirium, and it may produce dangerous respiratory depression. The combination of codein with one of the barbiturates is sometimes beneficial. Sleep should be promoted by hypnotic doses of amytal, chloral, or other simple hypnotic such as paraldehyde. The doses of these agents should be diminished as rapidly as conditions permit and they should be discontinued whenever possible. Their effectiveness is materially enhanced by psychotherapy and reassurance of the patient.

It should be emphasized that the necessity for operation, its comparative safety, and its beneficial results should be discussed with the patient at the very beginning of treatment. His written consent to operation should be secured at this time and the subject then should not be referred to again. In no event should the patient be harrassed by days of anticipation through knowing in advance the date of operation. It was Crile who first taught us the technique and importance of anoci-association and of the procedure dubbed "stealing the thyroid." The lessons learned from these two methods of procedure are as valid today as ever but the radical advances

which have been made in the field of the fixed anesthetics have largely supplanted Crile's more difficult and complicated methods by easier and simpler ones. When the day of operation comes he should be given a basal anesthetic before leaving his bed. The one to be used should preferably be determined in consultation with the surgeon as its choice is in part determined by the type of operation and whether anesthesia is to be local or general.

Diet should be prescribed carefully. Protein probably should be kept close to the basal requirements while carbohydrate is best given in abundance. In emaciated patients a high calory diet should be prescribed to improve nutrition and bring it as early to normal as possible. Patients with much edema should have a restricted salt and water intake, just as in any other type of congestive heart failure. An abundance of glucose should be given during the 24 hours just preceding operation. This is best administered in orange juice or other fruit drinks, and in candy. Abundant fluids must also be taken by the patient shortly before operation. These two steps contribute largely to the prevention of acidosis and dehydration.

Congestive heart failure is dealt with in the usual manner by the use of digitalis and diuretics in addition to the foregoing procedures. About 1.5 gm. (gr. xxij) of a standardized leaf may be given in the first 2 or 3 days, to be followed by maintenance doses of 0.1 to 0.3 gm. (gr. jss to gr. ivss) daily. Almost all patients respond to some extent. Many do so fairly satisfactorily; some to a moderate degree; and others only slightly. This is the case among both the fibrillators and those with regular sinus rhythm, though the former are rather more responsive than the latter. Where anasarca is pronounced resort to the diuretics is often necessary. In my experience much time may be saved by turning at once to the intravenous administration of mersalyl in doses of 0.1 to 0.2 gm. (1 to 2 cc. of the commercial 10% solution); repeated every 3 or 4 days if required. The supplementary administration of ammonium or calcium chlorid is desirable only in obstinate cases. Paracentesis of chest or abdomen rarely is necessary, but should be performed if indicated. Other remedies are in my opinion of value too doubtful to warrant their discussion.

The anginal type is commonly rather unresponsive to treatment by drugs. Immediate relief of the seizure may be had from the nitrites, but they often upset the patient through increasing the tachycardia, palpitation and nervousness, as well as by their common head phenomena in aggravated form. Digitalis is rarely of any value and is likely to increase the frequency, if not the severity of the pain. The greatest help is given by theobromin continued over a period of many days or weeks if well borne. It should always be tried but one should not place too much confidence in its efficacy.

Restoration of normal sinus rhythm is frequently possible in the presence of auricular fibrillation by the administration of quinidin. I do not, however, favor its pre-operative use because return of sinus

rhythm in these patients seldom contributes significantly to the relief of heart failure. Further, the auricular fibrillation often returns promptly following operation with its attendant manipulation of the thyroid gland. Last, many patients spontaneously resume normal rhythm within 10 days or less following thyroidectomy. Quinidin is best reserved for postoperative restoration of sinus rhythm in those patients whose fibrillation persists for more than 10 to 14 days. By so using it the normal rhythm is usually resumed promptly and permanently. In some patients the fibrillation is of the fixed type and in these it will either not be checked by quinidin or, if checked, will return shortly after withdrawal of the drug.

These therapeutic procedures should be followed faithfully and persistently so long as improvement in the patient's condition continues. When this point is reached the administration of iodin should begin and be continued until what is apparently optimal improvement has been secured—usually within 10 to 14 days—when the surgeon should take over the patient for immediate operation. The details of the administration of iodin are now so familiar to all that they need not be repeated. Suffice it to say that while Lugol's solution is the form in which it is most often given, the same results may be secured with any of the common preparations such as the syrup of hydriodic acid or the iodids of sodium or potassium. The dose should be adequate but need not be large. Maximal action is secured from 0.6 cc. (min. x) of Lugol's given 3 times daily, or an equivalent amount of iodin in the form of one of the other preparations mentioned.

The administration of iodin usually leads to prompt and rather striking further improvement in the patient's condition, primarily by diminution in thyroid intoxication. This is reflected in further subsidence of the cardiac manifestations. Where the response to other treatment has been more or less satisfactory the institution of iodin therapy may lead to dramatic betterment, often to well nigh complete restoration which, however, seldom endures for long. The marked tendency for the optimal effects of iodin to diminish rather quickly is the chief reason for deferring its use until the period just preceding operation. It is often stated that when one course of iodin has been given, a second is largely ineffective. This is not true in most cases, and if a few weeks be allowed to elapse between courses, the second is generally quite satisfactory in its effects. It must be admitted, however, that the results from the second course are sometimes inferior to those from the first.

The operation is now undertaken when the patient's recovery appears to be optimal, but medical treatment should be prolonged through the early postoperative period, at least to the extent of continuing the iodin, the sedatives as indicated, and the administration of digitalis if there be indications of returning heart failure. Wisdom often dictates the performance of a two-stage thyroidectomy. In this event some modification of the medical treatment may

be needed throughout the interval between the 2 operations. The first operation, being generally a hemithyroidectomy, often diminishes the thyrotoxicosis to such an extent that little or no interval medical treatment is required other than diet and the general building up of the patient's nutrition and strength.

Following the completion of subtotal thyroidectomy the most favorable cases will seldom require medical or other treatment beyond the first week, as their cardiac symptoms will have disappeared with the relief of the hyperthyroidism. In the less favorable group the physician will be left with the problem of dealing with one or another type of heart disease uncomplicated by thyrotoxicosis.

Summary and Conclusions. 1. Four clinical types of thyrocardiac are recognized: (*a*) Graves' disease with structurally normal heart; (*b*) Graves' disease in patients with rheumatic heart disease; (*c*) thyrotoxicosis in patients with arteriosclerotic or hypertensive heart disease; (*d*) patients with "masked hyperthyroidism."

2. Emphasis is laid upon thyrotoxicosis as the common factor primarily responsible for the cardiac manifestations in all four types.

3. The relatively unsatisfactory results of cardiac therapy are pointed out.

4. The keystone of successful treatment is shown to be the control of the thyrotoxic state.

5. The minimum of risk and the maximum of success are obtained by pre-operative medical treatment, subtotal thyroidectomy at the most favorable stage and postoperative medical treatment when necessary.

6. Close coöperation between the internist and the surgeon is essential.

HODGKIN'S DISEASE MISTAKEN FOR THYROID TUMOR.

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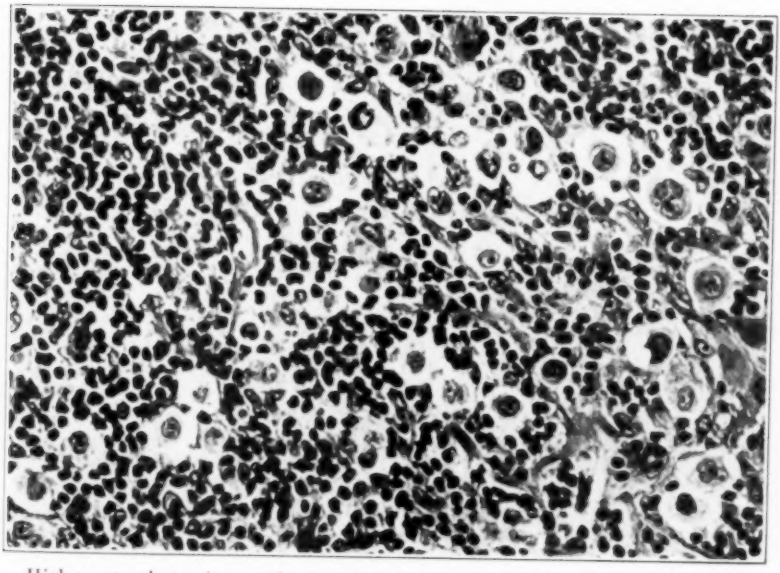
While the infrequency of involvement of the thyroid gland in Hodgkin's disease has been demonstrated in surveys by various authors,[1] it was actually not until the sporadic case reports of Krammer,[2] Lerman,[3] and Warnshuis,[4] that the possibility of mistaking Hodgkin's blastoma for thyroid struma was forcibly pointed out. In reviewing our records we find 2 cases in which such error was made. One of these cases was in the private service of one of the authors.

We shall attempt in this paper to discuss neither the pathology



High-power photomicrograph of section of mass removed in Case 2. This section demonstrates the marked pleomorphism of cells and the presence of large multinucleated cells with fibroblastic proliferation

nor the diagnosis of either thyroid tumors or Hodgkin's disease but merely to present briefly the case histories of these 2 cases and to discuss the importance of realization of the possibility of such diagnostic error.

Case Reports. CASE 1.—L. L., female, aged 17, was admitted to the private service of Dr. J. N. on July 4, 1931, with a tumor in the neck and the diagnosis of possible Hodgkin's Disease. History revealed the fact that the patient had first noted a mass in the left side of the neck a month prior to admission, that it had increased progressively in size but presented none of the symptoms of an acute inflammatory process. On physical examination one found a well-developed adult female showing no evidence of emaciation or thyrotoxicosis. There was noted a firm nodular mass in the left side of the neck apparently separated from the thyroid proper. The mass was freely movable, non-tender, and firm in consistency.

Laboratory findings at this time revealed a leukocyte count of 11,000, with 76 per cent polymorphonuclears, 22 per cent lymphocytes, 1 per cent monocytes and 1 per cent basophils. The urine was negative.

On February 5, 1933, the patient was operated upon, a low thyroid incision made, and the prethyroid muscles cut transversely. Two very firm masses, adherent to the surrounding muscles by dense fibrous tissue were found. One mass measuring 2 by 1 inches was located in the region of the left lobe of the thyroid, and the other measuring 1 by ½ inch in the region of the middle lobe. The operative diagnosis of malignancy of the thyroid gland was made and the patient returned from the operating room.

Subsequently the pathologic report of the tumors removed revealed a typical picture of Hodgkin's lymphoblastoma. Since that date the patient has run the usual malignant course of Hodgkin's disease.

CASE 2.—M. E., female, aged 46, admitted to the private service of Dr. M. D. on July 7, 1933, with a diagnosis of adenoma of the thyroid gland. On admission the patient complained of dyspnea and swelling of the neck of 2 weeks' duration accompanied by a hacking cough. She remained in bed from the time of onset until the time of admission. Her past history was essentially negative. On examination one found a well developed, moderately obese adult female showing no evidence of thyrotoxicosis. There was a firm mass felt in the region of the thyroid isthmus about 3 inches in diameter, which appeared to extend down behind the sternum. There were no other findings of significance.

The blood picture and urine examination on admission were of no significance.

The patient was operated upon on July 8, 1933, at which time thyroidectomy was attempted through a collar incision. The description of the findings at operation were as follows: "The middle lobe of the thyroid was of a hard, almost cartilaginous consistency. It was very firmly adherent to the neighboring structures. There was a distinct encapsulated area, containing some broken down inflammatory material which was in part suppurative in character. The right lobe also seemed enlarged but showed no evidence of any inflammatory process." The middle lobe was removed in small fragments, due to the inflammatory process, and a small portion of the right lobe in addition. The operative diagnosis at this time was subacute thyroiditis.

Cultures from the middle lobe failed to reveal the presence of any organisms. The pathologic diagnosis of the tissue removed was Hodgkin's lymphoblastoma with some thyroid tissue showing little evidence of colloid change.

Roentgen ray of the chest taken after the pathologic report revealed the presence of a mediastinal shadow, probably that of a mass of Hodgkin's nodes.

Discussion. While Hodgkin's lymphoblastoma of the thyroid gland is a rarity, Hodgkin's nodes are on the other hand very commonly situated in the region of the thyroid, as in the above 2 cases. In the first case the surgeon appreciated the clinical findings sufficiently to make a correct pre-operative diagnosis, but at operation the tumor was so closely related to the thyroid gland as to make him alter his diagnosis.

The justification for the presentation of these cases is not merely from the standpoint of description of the unusual, but rather to point out a condition which not infrequently leads to an incorrect diagnosis and consequently a very incorrect prognosis. The fact that the subsequent courses and ultimate prognoses of thyroid hyperplasia and Hodgkin's disease are so widely different makes the necessity of correct diagnosis of even greater importance than usual.

Summary. 1. Two cases of Hodgkin's disease of the neck mistaken for thyroid tumors are briefly presented.

2. The frequency of this location for Hodgkin's nodes and consequently the great possibility for mistaken diagnosis is pointed out.

3. The importance of correct diagnosis in this particular instance from a prognostic standpoint is emphasized.

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A CLINICAL COMPARISON OF A PURIFIED GLUCOSIDE AND WHOLE LEAF PREPARATIONS OF DIGITALIS.*

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The selection of the most effective digitalis preparation is a problem which constantly confronts the medical practitioner. Much

* A portion of the funds necessary for this study came from a grant by Hoffmann-La Roche, Inc.

of this perplexity may be relieved by sufficient careful clinical studies of the therapeutic efficacy of various preparations of the drug.

For many years the liquid preparations of digitalis have had widespread use because of historical reasons and official approval at a time when little was known about the chemistry of digitalis. Recently, however, through the realization that infusions and tinctures of the drug might fail in giving full therapeutic effects because of incomplete extraction of the active principles, preparations of the powdered whole leaf of digitalis in tablet, capsule or pill form have become more widely used. This trend has resulted in part from the recommendations of the Digitalis Committee of the American Heart Association.* Also, during the last few decades, there have appeared a number of special preparations containing only the active principles—the glucosides—of digitalis, claimed to be capable of effecting full therapeutic benefit in dosage more accurately measurable.

In view of the paucity of clinical studies comparing the relative merits of various digitalis preparations, the present study was undertaken in an effort to determine whether or not there is any difference in the therapeutic value of whole leaf as compared with a purified glucoside preparation of digitalis.

Method of Procedure. Ambulatory patients (25) with established auricular fibrillation, selected from the Adult Cardiac Clinic of the Pennsylvania Hospital, were divided into 3 groups, similar as to age and degree of circulatory efficiency. One group was given tablets of the whole leaf digitalis, the product of a well-established pharmaceutical house;† the second group received similar tablets prepared by the American Heart Association;‡ and to the third group were administered tablets containing only the extracted and purified glucosides§ of digitalis.

* Bulletin of the American Heart Association, May, 1930: (1) That tablets or capsules of powdered digitalis leaves be dispensed in all cases where digitalis is indicated, except in emergencies. (2) That such digitalis preparation be standardized by a recognized method of biologic assay, such as the cat or frog, for biologic potency, but that efforts be made to secure uniformity of activity, so far as possible, by adhering to one of these methods of standardization. (3) That the digitalis be further standardized for its absorbability and efficacy by administration to selected patients suffering with auricular fibrillation.

† Digitalis "Tabloids" (Burroughs, Wellcome) are made from the choice leaves of digitalis grown at the Wellcome Materia Medica Farm in England, and are assayed according to the U. S. P. method.

‡ These tablets were prepared under the supervision of Dr. Harry Gold in the Cornell Department of Pharmacology, as follows: 500 pounds of digitalis leaf, finely ground and dried, was obtained from an importer. A specimen was then tested in a few patients with auricular fibrillation in order to ascertain whether it was satisfactorily absorbed and whether it produced therapeutic effects in the average dosage. A portion of the total batch was then made up into compressed tablets by a tablet manufacturer, the strength of the tablets being ½, 1, 2 and 3 cat units, respectively. A sample of some of the tablets was then made into a tincture, and the latter again tested by the cat method in order to have an additional check on the potency of the tablets.

§ For the manufacture of Digalen Oral Tablets (Hoffmann-La Roche, Inc.) a quantity of digitalis leaf is dried, finely powdered and biologically assayed. From this quantity the beneficial active principles are extracted and purified by the method of Cloetta. The resultant purified substance is again biologically assayed. The dry powder consisting of the active glucosides is then made into tablets, so that each tablet is of ½ cat unit potency. The strength of the finished tablets is further checked by re-assay by the cat method.

Table 1 gives a summary of the 25 cases that were followed during the entire course of the study. These cases ranged in age from 23 to 79 years. There were 3 cases in the third decade, 6 in the fourth, 6 in the fifth, 6 in the sixth, 3 in the seventh, and 1 in the eighth. There were 16 males and 9 females. Rheumatic fever* was considered the underlying cause of the heart disease in 18 cases (72%); 2 of these cases also had hypertension and 1 had both hypertension and marked arteriosclerosis; arteriosclerosis was the etiologic agent in 6 cases (24%); 2 of these had associated hypertension; thyroid heart disease was present in 1 case (4%). The average age of the rheumatic group was 40 years; of the arteriosclerotic group, 62 years. In no case was syphilis considered to be an etiologic factor in the heart disease. A positive Wassermann reaction was present in only 1 case.

TABLE 1.—SUMMARY OF ETIOLOGIC FACTORS, PHYSICAL FINDINGS AND DIGITALIS DOSAGE IN 25 CASES OF ESTABLISHED AURICULAR FIBRILLATION.

Case.	Age.	Sex.	Etiologic classification.*	Congestive failure.	Vital capacity (av'ge).	Blood pressure (av'ge).	Average cardiac area (sq. cm.). Actual : predicted.	Daily maintenance dose of digitalis (grains).
7	42	F	Doubtful (M.S.)	++	1400	125/80	123 : 100	Dig 1½ : AHA 1½
16	28	F	Rheumatic fever (M.S.)	+	1800	110/75	125 : 90	Dig 1½ : AHA 1½
18	54	M	Arteriosclerosis	++	1900	190/110	175 : 106	Dig 1½ : AHA 1½
21	49	F	Doubtful (M.S.)	+++	2200	140/80	169 : 90	Dig 1½ : AHA 1½
23	53	F	Rheumatic fever (M.S.)	+	1300	160/60	141 : 80	Dig ¾ : AHA ¾
1	60	M	Rheumatic fever (M.S.)	+	3150	175/105	175 : 105	Dig 2 : BW 3
13	30	M	Rheumatic fever (M.S.)	+	2200	110/75	153 : 90	Dig 1½ : BW 1½
20	33	F	Doubtful (M.S.)	0	2000	90/60	90 : 92	Dig 1½ : BW 1½
22	50	M	Doubtful (M.S.)	0	2500	110/70	121 : 96	Dig 1½ : BW 1½
5	53	F	Rheumatic fever (M.S.)	++	1800	150/80	123 : 87	AHA ¾ : Dig ¾
9	46	M	Rheumatic fever (M.S.)	+++	2300	125/80	155 : 102	AHA 2½ : Dig 2½
10	45	F	Rheumatic fever (M.S.)	0	2000	170/100	119 : 92	AHA 1½ : Dig 1½
11	47	M	Arteriosclerosis (?)	+	2600	140/80	113 : 99	AHA ¾ : Dig ¾
17	79	M	Arteriosclerosis	+++	2100	180/80	167 : 111	AHA ¾ : Dig ¾
19	39	F	Doubtful (M.S.)	++	1400	110/60	133 : 90	AHA 1½ : Dig 1½
12	50	M	Thyroid	0	2700	125/75	114 : 95	AHA 1½ : BW 1½
14	38	M	Rheumatic fever (M.S. A.I.)	0	3400	120/70	129 : 107	AHA 3 : BW 3
24	67	M	Arteriosclerosis	++	1500	120/80	123 : 90	AHA 3 : BW 3
2	26	F	Doubtful (M.S.)	0	2800	105/65	165 : 108	BW ¾ : Dig 1½
6	69	M	Arteriosclerosis	++	2400	135/90	130 : 116	BW 2¼ : Dig 1½
8	31	M	Doubtful (M.S.)	0	2700	110/70	91 : 91	BW 1½ : Dig 1½
15	40	F	Doubtful (M.S.)	0	2200	120/70	114 : 99	BW 1½ : Dig 1½
25	36	M	Rheumatic fever (M.S.)	0	3100	120/65	101 : 106	BW 1½ : Dig 1½
3	23	M	Rheumatic fever (M.S. A.I.)	++	2600	120/35	105 : 104	BW ¾ : AHA ¾
4	58	M	Arteriosclerosis	0	2500	125/60	92 : 94	BW 3 : AHA 3

* No history of polyarthritis or chorea in cases classified as "doubtful."

M.S. = Mitral stenosis. A.I. = Aortic insufficiency. Dig = Digalen. BW = Burroughs, Wellcome & Co. AHA = American Heart Association.

The clinical course of the 3 groups was followed for 9 months on the 3 respective preparations of digitalis. During the subsequent 6 months, 4 of the 9 members of the group which had previously received the preparation containing only the glucosides were changed

* In this group are included all cases of mitral stenosis. Several of these cases who did not have a history of polyarthritis or chorea are classed etiologically as "unknown."

to the commercial whole leaf tablet, and the others were given the American Heart Association product; 5 of the 7 patients originally given the commercial whole leaf product were changed to the glucoside preparation, and the remainder was given the A. H. A. product; 6 members of the group started on the A. H. A. product were then placed on the glucoside tablet, and 3 were given the commercial whole leaf product. Each patient reported to the Cardiac Clinic at intervals of from 1 to 4 weeks for a check-up of symptoms and a physical examination, which included a vital capacity determination. Orthodiagraphic and electrocardiographic studies were made every 3 or 4 months.

TABLE 2.—RELATIONSHIP OF CARDIAC ENLARGEMENT AND CONGESTIVE FAILURE.

Degree of cardiac enlargement.	Total cases.	Degree of congestive failure.*	Cases.
1. Marked	10	Severe (+++)	3
		Moderate (++)	3
		Slight (+)	3
		None (0)	1
2. Moderate	11	Severe (+++)	0
		Moderate (++)	4
		Slight (+)	2
		None (0)	5
3. No enlargement	4	Severe (+++)	0
		Moderate (++)	0
		Slight (+)	0
		None (0)	4

* In none of the cases was the degree of congestive failure materially altered during the study.

In Table 2 the degree of cardiac enlargement is classified with signs of congestive failure. Râles at the lung bases, enlargement of the liver and edema of the lower extremities in addition to dyspnea on exertion were considered signs of congestive failure. In 4 cases (aged 31, 33, 36 and 58 years, respectively), there was no evidence of cardiac enlargement on physical or Roentgen ray examination. None of these 4 showed any signs of a failing circulation. In general, there seemed to be a direct relationship between the degree of cardiac enlargement and signs of congestive failure, in this small series.

The following case histories and clinical data are given in brief, as examples of the type of cases used and the character of the observations made.

Case Abstracts. CASE 6.—P. F., Jewish male, aged 69, of sthenic build, formerly a cabinet maker, with no history of illnesses etiologically associated with cardiac disease, first noticed fatigue, palpitation, dyspnea and orthopnea in 1922 (aged 56): He was enrolled in Cardiac Clinic in 1924, when marked cardiac enlargement, regular sinus rhythm, peripheral edema, normal blood pressure and pulmonary emphysema were found present. In October, 1925, he was admitted to the hospital in congestive failure, with auricular fibrillation; and digitalis therapy was instituted. At that time,

and on two subsequent hospital admissions (November, 1926, and June, 1927, respectively), regular sinus rhythm was restored (for periods of several months) by the use of quinidin. He has not been able to work steadily since 1925. On his last two hospital admissions (November, 1931, and January, 1933) he presented auricular fibrillation with symptoms of moderate cardiac failure.

Cardiovascular Diagnosis. (A) Arteriosclerosis, pulmonary emphysema; (B) cardiac enlargement, fibrosis of myocardium, left ventricular preponponderance; (C) chronic auricular fibrillation; (D) Class 2b.

CASE 6: P. F., WHITE MALE, AGED 69, MARRIED.

Etiologic classification:	Arteriosclerosis.					
Brand of digitalis:	Burroughs, Wellcome & Co.			Digalen.		
Date:	3/10/32.	6/16/32.	10/6/32.	1/12/33.	2/2/33.	4/6/33.
Average daily dose (gr.)	2¼	2¼	2¼	*	1½	1½
Weight (lbs.)	209	196	197	193	186½	193¾
Ventricular rate	82	86	72	168	92	84
Pulse rate	82	70	72	96	92	84
Dyspnea	++	++	0	++++	+	+
Edema	0	0	0	0	0	0
Lungs (râles)	0	0	0	++	0	0
Liver (cms. palp. M. C. L.)	0	0	0	0	0	0
Blood pressure	138/90	140/90	135/90	..	134/80	140/90
Vital capacity (cc.)	2350	2200	2600	1600	2600	2400

* The patient, having neglected to take digitalis for 3 weeks, was hospitalized on this date because of signs and symptoms of early congestive failure.

CASE 15.—B. K., an obese, Hungarian housewife, aged 40, with no history of illnesses etiologically associated with heart disease, had no cardiac symptoms until February, 1930. At that time—during the last month of a pregnancy—she developed palpitation, orthopnea and peripheral edema; and physical examination revealed auricular fibrillation with a short, soft, blowing diastolic murmur at the apex. Digitalis therapy, started at that time, has been continued without interruption. She has attended Cardiac Clinic since March, 1930. During the past 3 years she has been able to perform her household duties, complaining only of easy fatigue and slight dyspnea on exertion.

Present Cardiovascular Diagnosis. (A) Unknown; (B) mitral stenosis, cardiac enlargement, left ventricular preponderance; (C) chronic auricular fibrillation; (D) Class 2a.

CASE 15: B. K., WHITE FEMALE, AGED 40, MARRIED.

Etiologic classification:	Unknown (mitral stenosis).					
Brand of digitalis:	Burroughs, Wellcome & Co.			Digalen.		
Date:	12/10/31.	3/24/32.	7/14/32.	10/20/32.	1/19/33.	4/13/33.
Average daily dose (gr.)	2.25	1.07	1.07	1.07	1.07	1.07
Weight (lbs.)	203	192¾	184½	189½	198½	190½
Ventricular rate	84	70	72	76	64	76
Pulse rate	84	70	72	76	64	76
Dyspnea	0	0	0	0	0	0
Edema	0	0	0	0	0	0
Lungs (râles)	0	0	0	0	0	0
Liver (cms. palp. M. C. L.)	0	0	0	0	0	0
Blood pressure	135/80	145/85	130/85	120/70	120/74	120/72
Vital capacity (cc.)	2400	2100	2550	2100	2200	2300

CASE 16.—M. L., a Jewish housewife, aged 28, with a history of tonsillitis at 10 years, rheumatic fever at 14 and 18 years, and attacks of pneumonia at 18, 19 and 20 years, respectively. Directly after the second attack of rheumatic fever, 2 weeks (January 14 to February 4, 1923) were spent in the hospital suffering palpitation and orthopnea. Physical examination revealed mitral stenosis, mitral insufficiency and cardiac enlargement; and digitalis therapy was begun. In November, 1928, she was enrolled in the Cardiac Clinic. In June, 1929, she suffered left hemiplegia, which completely disappeared within 36 hrs. In May, 1930, right hemiplegia with motor aphasia developed; and the aphasia has persisted to date. Auricular fibrillation was first diagnosed in July, 1929. During the past few years she has been kept fairly free of congestive phenomena under digitalis therapy; but her exertion tolerance is very poor.

Present Cardiovascular Diagnosis. (A) Inactive rheumatic fever; (B) mitral stenosis, mitral insufficiency, cardiac enlargement; (C) chronic auricular fibrillation; (D) Class 2b.

CASE 16: M. L., WHITE FEMALE, AGED 28, MARRIED.

Etiologic classification:	Rheumatic fever.					
Brand of digitalis:	Digalen.			Am. Heart Assn.		
Date:	12/17/31.	3/17/32.	7/7/32.	10/6/32.	1/5/33.	4/13/33.
Average daily dose (gr.)	1½	1½	1½	1½	1½	1½
Weight (lbs.)	126	127¼	123¼	126½	126	125½
Ventricular rate	80	68	80	96	80	84
Pulse rate	80	62	74	96	80	84
Dyspnea	0	0	0	0	0	0
Edema	0	0	0	0	0	0
Lungs (râles)	0	0	0	0	0	0
Liver (cms. palp. M. C. L.)	0	0	0	0	0	0
Blood pressure	126/72	125/75	118/68	120/70	125/78	105/65
Vital capacity (cc.)	1800	1500	1600	2000	1600	1900

BIOASSAY. To make certain of the potency of the preparations used, Dr. John Reisinger, of the Pharmacology Department of the University of Pennsylvania kindly performed a bioassay of the 3 preparations used in the clinic. The potency was not compared with any standard preparation such as the International Digitalis powder, but simply the relative potencies of the 3 preparations per tablet. In the case of Digalen, the manufacturers state the potency in cat units per tablet, and our results are expressed as the number of tablets per cat unit and as a fraction of a cat unit per tablet. The potency of the other preparations is similarly expressed as a fraction of a cat unit per tablet since the drugs were dispensed on the assumption that each tablet contained 0.1 gm. digitalis with a potency of approximately 1 cat unit.

The cat method technique of C. de Lind van Wijngaarden (*Arch. exp. Path. u. Pharmakol.*, **113**, 40, 59, also **114**, 21, 1926) as described by Burns (*Methods of Biological Assay*, Oxford University Press, 1926) was used. The average lethal dose per kg. of cat of a hot water infusion for 5 cats is given for each preparation expressed in grams of the powdered tablet or in the number of tablets in the case of Digalen, since each tablet is said to contain ½ cat unit. The probable error is expressed as twice the standard deviation.

Preparation.	Lethal dose per kg. of cat. Powdered tablet.	Weight of tablet.	Cat units per tablet.	Relative potency.
American Heart Association	0.165 gm. ± 0.033	0.113 gm.	0.68	70%
Burroughs, Wellcome & Co.	0.185 gm. ± 0.045	0.160 gm.	0.86	89%
Digalen	2.06 tablets ± 0.40	"½ CU" (Manufacturer's assay)	0.48	100%

This assay indicates that the Digalen tablets under our laboratory conditions were practically the strength claimed for them by the manufacturers; namely, ½ cat unit per tablet. The A. H. A. and Burroughs, Wellcome tablets used contained less than 1 cat unit each and, compared with 2 tablets of Digalen (1 cat unit) as 100%, were 70% and 89% as potent, respectively.

Results. No striking difference was observed in the general clinical picture, including the ability to work, of the members of the 3 groups. However, during the course of the study, before the summarization of our results, and before bioassay was done, it was our impression that the preparation of the extracted purified glucosides was somewhat more effective per *stated* unit of dosage than either of the two whole leaf preparations. Final analysis of the data tended to substantiate that idea, since in 5 (25%) of the 20 cases given the purified glucoside preparation the daily maintenance dosage, measured in cat units, was smaller than that of either of the whole leaf preparations. This result may be explained by the relatively greater strength of the purified glucoside tablet as revealed by the bioassay. No difference was detected in the dosage per cat unit of the two whole leaf preparations.

The progress of each case was based upon the sense of well-being, the ventricular rate, the pulse deficit, the physical signs of congestive failure, and the vital capacity. In the cases with increase of congestive failure, a relationship was observed between the diminution of vital capacity on the one hand, and the increase in weight, with edema and hepatic engorgement, on the other. No consistent significant changes were observed in the orthodiagraphic studies. We appreciate that such uncontrollable factors as the progression of the pathologic lesions, lack of coöperation in following the prescribed dosage of digitalis or the suggested amount of physical effort, and the development of concomitant infections may affect the circulatory reserve and render the interpretation of results difficult.

In making such a study it must be remembered that there exists in the majority of patients with established auricular fibrillation a fairly wide margin between the minimum dosage necessary for optimum digitalization and the maximum dosage which can be tolerated without the incidence of toxic effects.

Since the bioassay reveals a greater potency per unit of dosage in the case of the purified glucoside preparation, it is impossible to determine whether the slightly smaller cat unit dosage necessary with this preparation, in a few cases, was the result of this factor or of better absorption, better fixation in the heart muscle or a combination of these factors.

Summary and Conclusions. 1. Twenty-five ambulatory cases of established auricular fibrillation were divided into three similar groups: one group was given a preparation of the extracted, purified glucosides of digitalis; another was given a whole leaf preparation

manufactured by a well-established pharmaceutical house; and the third group received whole leaf tablets prepared by the American Heart Association. The groups were followed clinically for 9 months and then, after interchanging the preparations, for another period of 6 months.

2. No significant difference could be ascertained in the clinical pictures of the patients in the 3 groups during the period of observation.

THE MECHANISM OF THE EARLY RELIEF OF PAIN IN PATIENTS WITH ANGINA PECTORIS AND CONGESTIVE FAILURE AFTER TOTAL ABLATION OF THE NORMAL THYROID GLAND.*†

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We wish to report observations on the mechanism of the early relief of pain in many patients with angina pectoris and congestive failure immediately after complete removal of the normal thyroid gland. Three syndromes were studied: the characteristic syndrome of angina pectoris (Heberden), precordial pain other than angina and the hyperesthesia and hyperalgesia of the chest wall frequently associated with the various forms of chronic heart disease. In accord with the clinical studies of the circulation which formed a rational basis for removal of the normal thyroid gland in congestive failure and angina pectoris,[6–10] the most striking relief of chest pain has been concomitant with the lowering of the metabolic rate and decrease in the work of the heart as gauged by measurements of the velocity of blood flow.[3, 11, 12, 22] Not infrequently, however, chest pain, experienced constantly for months to years, has disappeared immediately after operation when the metabolic

* This is the sixth study of the treatment of chronic heart disease by producing a subnormal metabolic rate in patients with no evidence of thyrotoxicosis.

† Read in part at the meeting of the American Society for Clinical Investigation at Atlantic City, April 30, 1934.

rate was still unchanged. Of 50 patients with angina pectoris or congestive failure, 20 definitely have shown this early postoperative relief of pain. The present communication deals with observations only on these patients.

The effect of operation on the distribution of pain and on other characteristics of the attacks was studied when the patients were exercised under standardized conditions.[44] Precordial pain other than that characteristic of angina pectoris was experienced at complete bed rest in almost all of the 20 cases of congestive heart failure and angina pectoris. The pain varied in character and location in different patients and was characterized as "dull," "heavy," "gripping," "tender," "pressing," "knife-like," "crushing," "tearing," "sticky like needles." It was referred to the sternum, the xyphoid, the left or right chest. The areas of skin hyperesthesia and muscle tenderness varied greatly in extent, in some patients being narrowly localized, in others being rather widespread. In a given patient, however, the characteristics of the painful areas were constant. These symptoms have long been accurately described by clinicians, particularly by Morgagni,[41] Laennec,[30] Hope,[27] Gibson,[23] Mackenzie,[35] Lewis,[33] White[56] and Swetlow.[50]

Methods. Observations on the radiation of pain and the symptom complex of angina pectoris were made immediately after an attack had been produced by exercise in the cold. These observations were verified frequently before and after operation. The observations reported on non-anginal precordial pain were made only on patients who could be relied on for accurate and intelligent reports and in whom there was no evidence of other etiological factors. The type, frequency, duration and intensity of such precordial pain were particularly noted. The observations were made independently by several observers and were checked repeatedly before and after operation. Every attempt was made to avoid suggestion during examination or interrogation. Skin hyperesthesia was tested by cotton, pinch, scratch and pin prick. Hyperalgesia of the thorax was tested by finger pressure; muscle tenderness was tested by pinching.

The early postoperative relief of pain is exemplified by the clinical course of patient G. F., the first patient in whom complete removal of the normal thyroid gland was performed for relief of angina pectoris and congestive heart failure.[11]

Clinical Abstract. For many months this patient (G. F.) had suffered attacks of stabbing pains over the left precordium and scapula, radiating over both shoulders and down the inner aspects of both arms. The pain was increased by exercise, diminished by rest and relieved by nitroglycerin. During the 6 months prior to admission this patient also noted a constant sense of pressure in the chest and continuous ache over the precordium. Immediately after operation all the above-mentioned pains vanished. The pains remained absent, although no sedative was administered after the 3d postoperative day. The basal metabolic rate on the 7th postoperative day was −7%, as compared with the pre-operative rate of −2%. Between the 2d and 5th postoperative week the pain on exercise referable to the left shoulder recurred, but disappeared permanently as the basal metabolic rate fell to −28%.

TABLE I.—EARLY RELIEF OF PAIN IN CHRONIC HEART DISEASE.

TABLE 1.—EARLY RELIEF OF PAIN IN CHRONIC HEART DISEASE.

Case.	Date of operation.	Age, yrs.	Diagnoses.*	Pre-op. B.M.R., %	Pre-operative chest discomfort.	Observed disappearance of pain postoperative.†		Partial or complete recurrence of pain postoperative.		Final disappearance of pain postoperative.	
						Time.	B.M.R., %	Time.	B.M.R., %	Time.	B.M.R., %
1. G. F.	12/15/32	52	Rheumatic heart disease; congestive failure; coronary thrombosis and angina pectoris	−2	Constant pain over sternum and stabbing over precordium to left scapula; ache in both arms, even at rest (2 yrs.)	1 day	−7 1 week post-op.	14 days	−10	5 weeks	−28
2. E. W.	11/21/33	27	Rheumatic heart disease; congestive failure	+5	Frequent palpitation and precordial pain (3 yrs.)	3 days	+5 11th day	None	...	...	...
3. R. D.	3/25/33	22	Rheumatic heart disease; auricular fibrillation; congestive failure	−3	Constant pressure over precordium at rest (10 yrs.)	2 days	...	None	...	...	...
4. F. C.	4/18/33	31	Cor pulmonale; congestive failure	−4	Pounding, constant sense of pressure pain over heart at rest (5 yrs.)	4 days	−10 10th day	None	...	...	...
5. W. B.	7/ 6/33	64	Arteriosclerotic heart disease; congestive failure	−10	Pounding of heart, continuous stabbing ache over precordium at rest (1 yr.)	3 days	...	15 days	...	8 weeks	−32
6. F. Z.	9/14/33	21	Rheumatic heart disease; cardiac asthma	−1	Intense substernal constriction, pain, severe dyspnea occurring at rest (8 mos.)	4 days	...	...	...	...	...
7 B. R.	7/28/33	48	Rheumatic heart disease; congestive failure	+3	Tightness of chest and "bearing down feeling" over precordium at rest (2 yrs.); stabbing pain over left breast (3½ yrs.)	1 day	−10 30th day	None	...	...	...
8. M. C.	7/21/33	57	Arteriosclerotic heart disease; angina pectoris; coronary thrombosis	−24	Dull ache in left shoulder; steady pain over precordium at rest (3 yrs.)	1 day	−26 12th day	12th week	−34	...	...
9. M. F.	6/30/33	50	Arteriosclerotic heart disease; angina pectoris; coronary thrombosis	−14	Sharp precordial pain following small meals (2 yrs.); precordial pain at rest daily	1 day	−17 16th day	9th day	...	4 weeks	−31
10. F. D.	8/25/33	18	Rheumatic heart disease; congestive failure	−12	Sharp "stabbing" precordial pain pounding when lying on left side (16 mos.)	1 day	...	...	...	...	...
11. G. O.	7/31/33	65	Hypertensive heart disease; angina pectoris	−13	"Bands across chest" 5 to 6 times a day at rest; knife-like pain in back after meals (8 yrs.)	1 day	...	12 days	...	8 weeks	−35
12. M. W.	7/24/33	54	Arteriosclerotic heart disease; angina pectoris; coronary thrombosis	−7	Substernal pressure, "choking feeling" attacks of pain at rest over precordium "like knife put in and turned" (8 yrs.)	1 day	−12 10th day	None	...	...	...
13. H. G.	8/26/33	22	Rheumatic heart disease; congestive failure	+7	Sharp "sticky" pain over heart, coming on 1 to 2 times a day while at rest (1 yr.)	1 day	...	None	...	...	...
14. G. M.	12/15/33	45	Rheumatic heart disease; congestive failure	−6	Marked tenderness to pressure over localized area, 5th rib anteriorly	2 hours local anes.	−11 8th day	None	...	...	...

* All patients with rheumatic heart disease showed the signs of mitral stenosis.
† The "Time of Disappearance of Pain" refers to time at which first observations were made.

A resumé of our findings in regard to the early relief of non-anginal precordial pain in 14 patients after complete ablation of the thyroid gland is given in Table 1. Of the 14 patients, 9 experienced unquestioned relief within 24 hours after operation; in 4 of the 14, pain recurred within a few weeks, followed by permanent disappearance at varying intervals of time as the basal metabolic rate dropped. In 1 patient (M. C.), the basal metabolic rate was low before operation and showed only a moderate further reduction. The precordial pain in this subject persisted except for a period of marked relief during the first postoperative week.

As an increasing number of patients stated that precordial pain disappeared soon after operation, it became difficult to believe that this relief was due to suggestion. The influence of postoperative sedation was eliminated as a causal factor. The possible effects of general anesthesia were obviated by examination within 2 hours after operation conducted under local novocain infiltration. These observations led us to review the current concepts of the nature of precordial pain in patients with chronic heart disease.[19, 29, 34, 35]

It is generally held that the symptom complex of angina pectoris and precordial pain and chest hyperalgesia in other forms of chronic heart disease have a common underlying neural pathway. Under normal physiologic conditions, a constant stream of impulses is conveyed by the visceral afferent nerves from the heart to the spinal cord. If, because of a cardiac lesion, excessive stimuli bombard a certain segment of the spinal cord, an irritable focus is produced in the nerve centers of the segment. Normal afferent impulses from skin and muscle of the chest wall that happen to traverse this same irritable cord segment become augmented. It is these impulses that are appreciated in the sensorium as pain. Since these impulses normally travel from the chest wall to the spinal cord, the pain is naturally referred to the chest. Further stimulation of such skin areas by touch or pressure merely augments the normal skin impulse; and heightened sensitivity, hyperesthesia or actual tenderness is thus produced. If cardiac afferent pathways are interrupted, the "irritable focus" subsides and hyperalgesia and pain disappear.

The hypothesis that the early relief of hyperesthesia and hyperalgesia of the chest is due to interruption of cardiac afferent nerve pathways was tested by more detailed pre-operative and post-operative studies in several patients. Three intelligent and coöperative patients who were chosen had severe localized symptoms and signs. One patient suffered from angina pectoris, another from angina pectoris and congestive heart failure and the 3d from angina pectoris induced by attacks of paroxysmal auricular fibrillation. The night before operation, each of the areas of skin sensitivity and spots of local tenderness were accurately mapped out with indelible ink. Two, and again 9 hours after operation, observations were made by different observers on changes in hyperesthesia and

hyperalgesia. These observations were repeated daily during the patient's stay in the hospital. A brief resumé of our findings is given below:

CASE 15.—*Rheumatic heart disease, mitral stenosis and insufficiency, paroxysmal auricular fibrillation. Loss of hyperesthesia and diminution in hyperalgesia of the chest after total thyroidectomy. Return of all signs in 22 days before basal metabolic rate dropped. Permanent loss of hyperesthesia and hyperalgesia coincidental with fall in basal metabolic rate.* M. G., a female, aged 49, was admitted with the diagnoses of rheumatic heart disease and paroxysmal auricular fibrillation. She complained of severe "pressing and crushing" epigastric pain, radiating to both scapulæ and associated with a "choking" sensation in the neck, combined with the paroxysmal auricular fibrillation. Examination showed hyperesthesia and areas of localized precordial tenderness. (Fig. 1, *a*.) Light pressure on these areas made her wince. Pre-operatively, the basal metabolic rate was +3%.

Two hours after operation, performed under local anesthesia, November 24, 1933, the patient developed paroxysmal fibrillation, associated with an "uncomfortable" feeling under the sternum. She was surprised to note that for the first time in 2 years the attack was not accompanied by crushing pain. Pressure over spots, previously very tender, gave rise only to a dull ache. Hyperesthesia over the left chest anteriorly and posteriorly had disappeared completely. (Fig. 1, *b*.) During the next 10 hours the patient was given no sedation. At 9 P.M., on the day of operation, the patient was alert and the above-mentioned observations were corroborated. These findings remained constant during the next 10 days, examination being made in the morning and late afternoon. She stated that "her heart felt quieter and lighter." From the 11th to the 22d day after operation, hyperesthesia and tenderness over localized bone areas gradually returned to their pre-operative intensity. (Fig. 1, *c*.) Periosteal hyperalgesia and skin hyperesthesia were present as before operation. Seven weeks after operation, hyperesthesia and hyperalgesia had disappeared. The basal metabolic rate at this time was −16%.

CASE 16.—*Coronary sclerosis, angina pectoris of 2 years' duration. Loss of hyperesthesia after total thyroidectomy. Loss of hyperalgesia of bone and muscle coincident with fall in basal metabolic rate.* M. S., male, aged 46, entered the hospital because of attacks of "crushing," viselike pain under the xyphoid, radiating to the back and left arm, associated with a "choking" sensation in the throat brought on by exertion, emotion and ingestion of food. On examination the left chest anteriorly and posteriorly was hyperesthetic to pin prick, cotton, pinch, heat and cold. A spot painful to pressure was present over the left 4th rib anteriorly. (Fig. 2, *a*.) The left sternomastoid and trapezius muscles were tender to pressure. The basal metabolic rate pre-operatively was −8%. Nine hours after operation (November 25, 1933, gas-oxygen), the skin hyperesthesia had disappeared but the bone and muscle tenderness were still present. (Fig. 2, *b*.) This finally disappeared 21 days postoperatively, when the basal metabolic rate had decreased to −18%. (Fig. 2, *c*.)

CASE 17.—*Rheumatic heart disease, mitral stenosis and regurgitation. Loss of hyperesthesia and hyperalgesia of chest after left hemithyroidectomy. Return of all signs 6 weeks after operation.* R. S., a male, aged 41, was admitted with the diagnoses of mitral stenosis and regurgitation, aortic insufficiency, coronary thrombosis and angina pectoris. The pre-operative distribution of skin hyperesthesia, bone and muscle tenderness is indicated in Fig. 3, *a*. The basal metabolic rate was +8%. On November 28, 1933, the left lobe of the thyroid gland was removed under local novocain anesthesia. Two hours after hemithyroidectomy, hyperesthesia and muscle tenderness had disappeared. (Fig. 3, *b*.) After 2 weeks there was a

gradual return of hyperesthesia and hyperalgesia until all signs had returned to their pre-operative level. (Fig. 3, *c*.) Six weeks after operation, the basal metabolic rate was +3%.

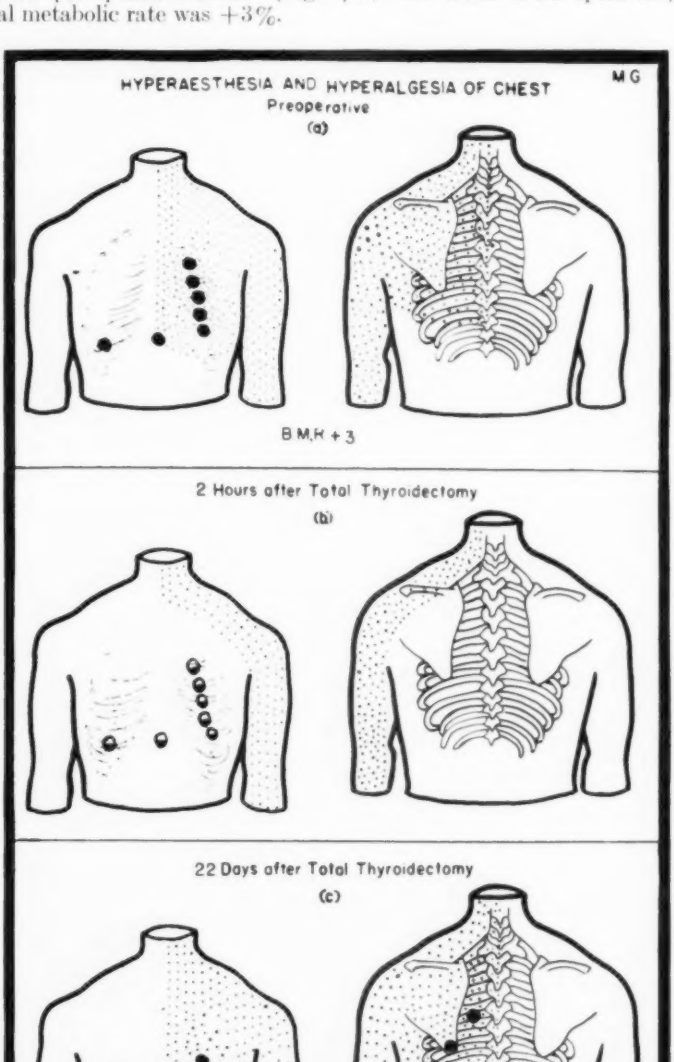

FIG. 1.—Case 15. Loss of hyperesthesia of chest immediately after total thyroidectomy with return of skin hypersensitivity 11 to 22 days postoperatively, before the basal metabolic rate had dropped markedly. Dots indicate regions of hyperesthesia; solid black areas indicate points of bone tenderness. Circles indicate lessened periosteal tenderness.

These 3 patients showed prompt relief of hyperesthesia, hyperalgesia and muscle tenderness referable to certain localized areas, which had been regularly present before operation. These areas

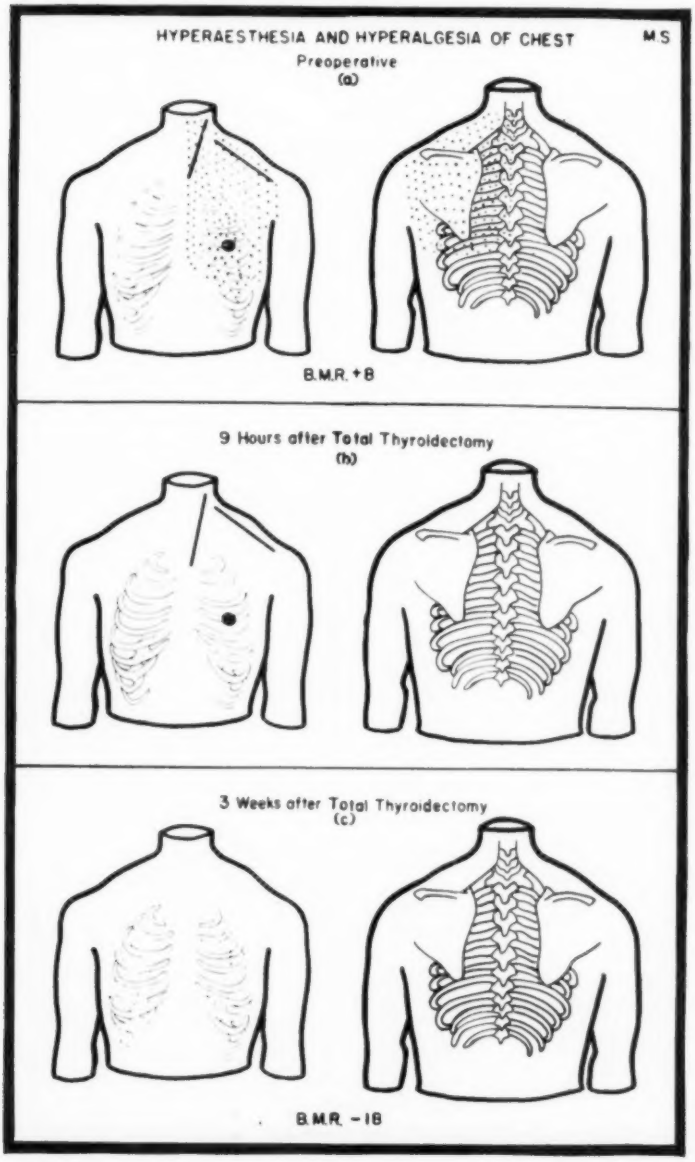

FIG. 2.—Case 16. Immediately after total thyroidectomy, persistent loss of hyperesthesia. Loss of muscle and bone tenderness coincident with reduction of the basal metabolic rate. Dots indicate regions of hyperesthesia; solid black area indicates bone tenderness. Lines indicate muscle tenderness.

again became hyperesthetic a few weeks after total thyroidectomy. Only after the basal metabolic rate showed a marked lowering did hyperesthesia and hyperalgesia disappear permanently.

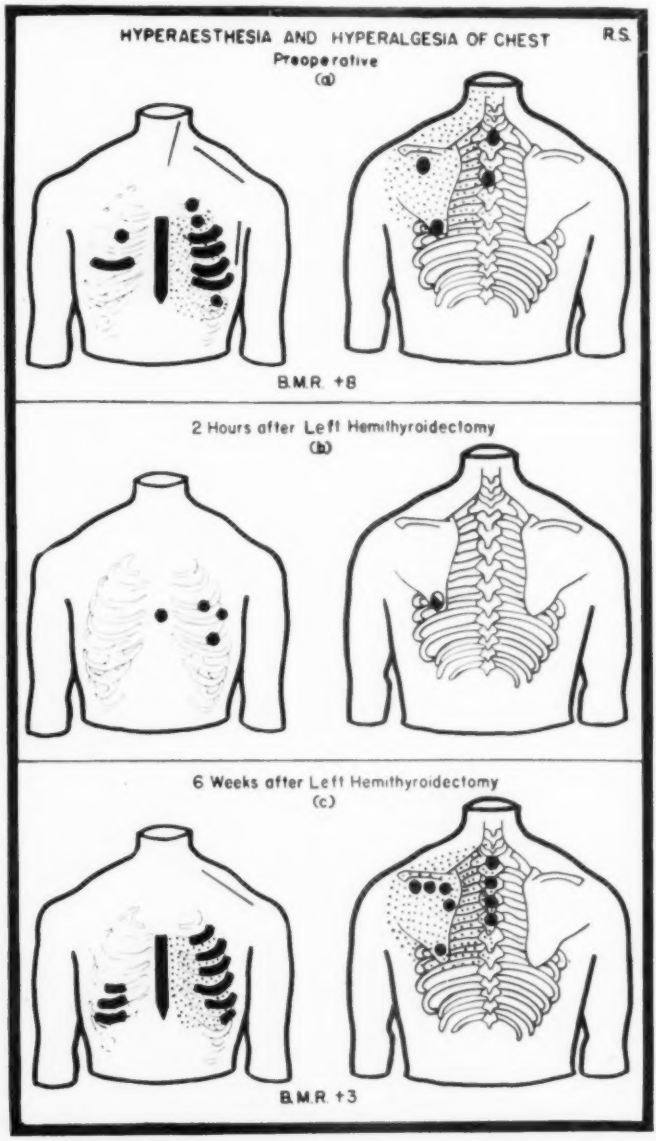

FIG. 3.—Case 17. Immediately after left hemithyroidectomy, loss of hyperesthesia and hyperalgesia with partial return of symptomatology 6 weeks postoperatively. Dots indicate regions of hyperesthesia; solid black areas indicate regions of local bone tenderness.

Observations on the early relief of pain in the patients presented in Table 1, and the sudden loss of hyperesthesia and hyperalgesia in patients M. G., M. S. and R. S., resembled the findings of others following cervical sympathectomy or paravertebral alcohol injection for relief of pain in angina pectoris.[40, 43, 50, 55] In patients with bilateral angina pectoris it has been observed[54] that unilateral cervical sympathectomy usually results in freedom from pain only on the operated side. If the early relief of pain after total thyroidectomy were due to interruption of nerve pathways, it was felt that after hemithyroidectomy patients might likewise show a unilateral loss of the pain of angina pectoris on the operated side. Three patients were studied in whom only one lobe of the thyroid was removed. Two-stage operations were indicated in these patients for reasons which will be outlined in forthcoming communications. Pre-operatively, each of the 3 patients showed accurately reproducible attacks of angina pectoris with pain referred to both sides of the chest and over the inner aspects of both arms.

CASE 18.—*Coronary sclerosis, bilateral angina pectoris. Loss of angina in right chest and arm after right hemithyroidectomy. Partial return of symptoms in 7 weeks. Loss of angina in left arm and chest after left hemithyroidectomy.* M. H., a male, aged 54, entered the hospital because of angina pectoris of 2 years' duration, due to arteriosclerotic heart disease. The attacks appeared only on exertion, with knifelike pain over the precordium, radiating to the sternum, right chest, both scapulæ, inner aspects of both arms, the throat and both sides of the neck and face. (Fig. 4, *a*.) Characteristic attacks were precipitated regularly after 52 to 57 trips on the staircase under the standard conditions described elsewhere. The basal metabolic rate before operation was +5%.

At operation (October 16, 1933), only the entire right lobe of the thyroid was removed. The next day the patient spontaneously stated that for the first time in many months the right chest felt "free of pain and oppression." The left chest still felt "heavy and filled with discomfort." Two weeks after operation, the basal metabolic rate was unchanged, and attacks of angina pectoris were precipitated by exercise (57 trips on the staircase). The patient was surprised, however, that in contrast to the pre-operative bilateral distribution of the crushing pain he had always experienced, after right hemithyroidectomy no pain was experienced in the right chest, shoulder and neck. Pain was experienced only in the left chest, shoulder and arm, and terminated sharply at the midline of the chest. (Fig. 4, *b*.) During the next 4 weeks after discharge, the patient reported that attacks of angina, precipitated by walking in the street, were felt only in the left chest and arm. From the 5th to the 7th week, the patient noticed a gradual extension of pain to the right chest and shoulder and a return of pressure on the right chest during attacks of angina.

Seven weeks postoperatively, while walking, the patient developed an attack of angina pectoris, which gave rise to pain on the right as well as on the left side of the chest, anteriorly and posteriorly. It was similar in severity to those experienced before right hemithyroidectomy. The sense of oppression over the right chest returned, though definitely decreased compared to its intensity before operation. These characteristics of the spontaneous attacks were corroborated by similar attacks reproduced after 52 trips on the staircase under standard conditions. On January 8, 1933, left hemithyroidectomy was performed. On the same day of operation

the patient noted the absence of precordial pain which had been present pre-operatively and was not associated with exertion. Two weeks after operation the patient made 84 trips on the staircase without developing pain in the chest or arms. After exercise was over, a sense of pressure developed in both sides of the chest. The basal metabolic rate at this time was −4%.

CASE 19.—*Coronary thrombosis, bilateral angina. Loss of angina in left arm and chest after left hemithyroidectomy. Return of symptoms in 21 days.*

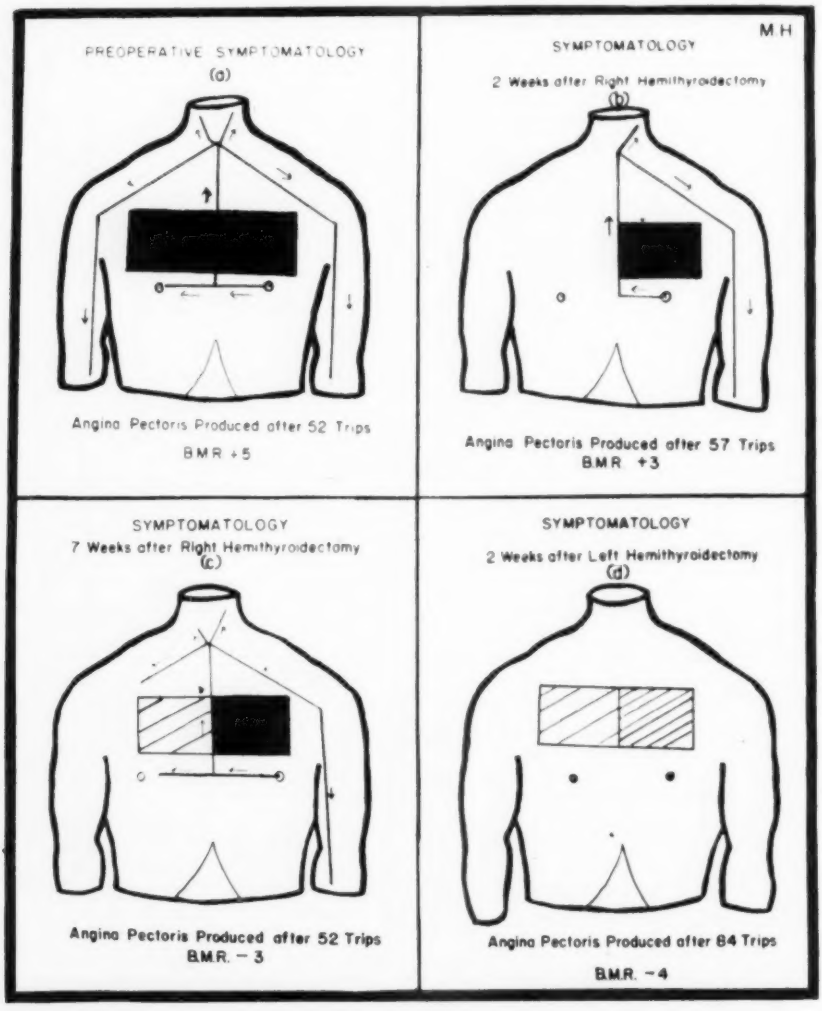

FIG. 4.—Case 18. After right hemithyroidectomy, loss of pain and oppression of angina pectoris experienced in right chest and arm. Return of symptoms 7 weeks after operation. After left hemithyroidectomy, complete loss of anginal pain and diminution in oppression. Lines indicate radiation of pain; blackened areas indicate oppression; hatched areas indicate diminution in oppression.

S. F., a male, aged 53, entered the hospital with the diagnoses of healed coronary thrombosis and angina pectoris. For 2 years walking a block always gave rise to crushing substernal pain, radiating to both chests, to the jaw, down both arms and to both scapulæ. The pain always lasted 5 to 15 minutes and was regularly accompanied by an intense choking and

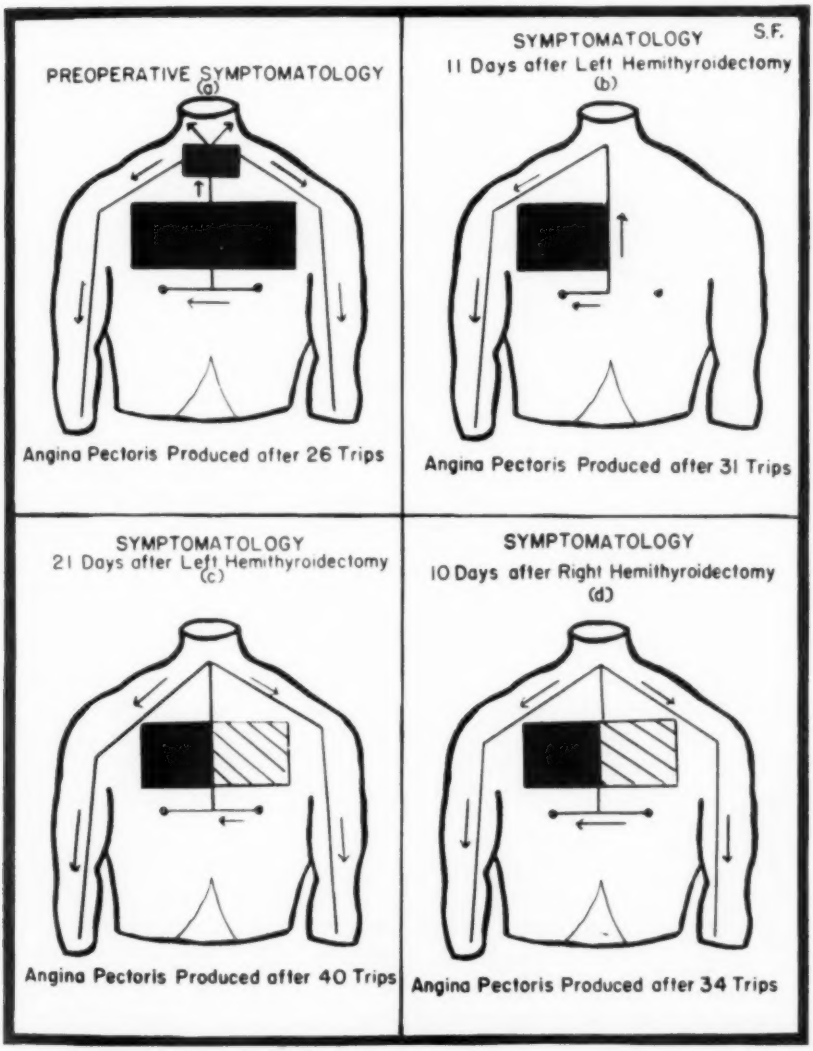

FIG. 5.—Case 19. After left hemithyroidectomy, loss of pain and oppression in right chest and arm. Twenty-one days after operation, return of symptoms. No changes in symptoms immediately after right hemithyroidectomy. Lines indicate radiation of pain; blackened areas indicate oppression; hatched areas indicate diminution in oppression.

gripping sensation over the throat. These attacks could be precipitated by exercise in the cold (31 trips on the staircase). (Fig. 5, *a*.) On November 7, 1933, a left hemithyroidectomy was performed. Five days later the patient experienced a characteristic attack of angina pectoris while at complete rest, except that for the first time in 2 years no pain whatsoever was referable to the left arm or chest. During the 2d postoperative week, similar attacks occurred, precipitated by exercise in the cold (31 trips on the staircase) (Fig. 5, *b*), no discomfort being experienced over the left

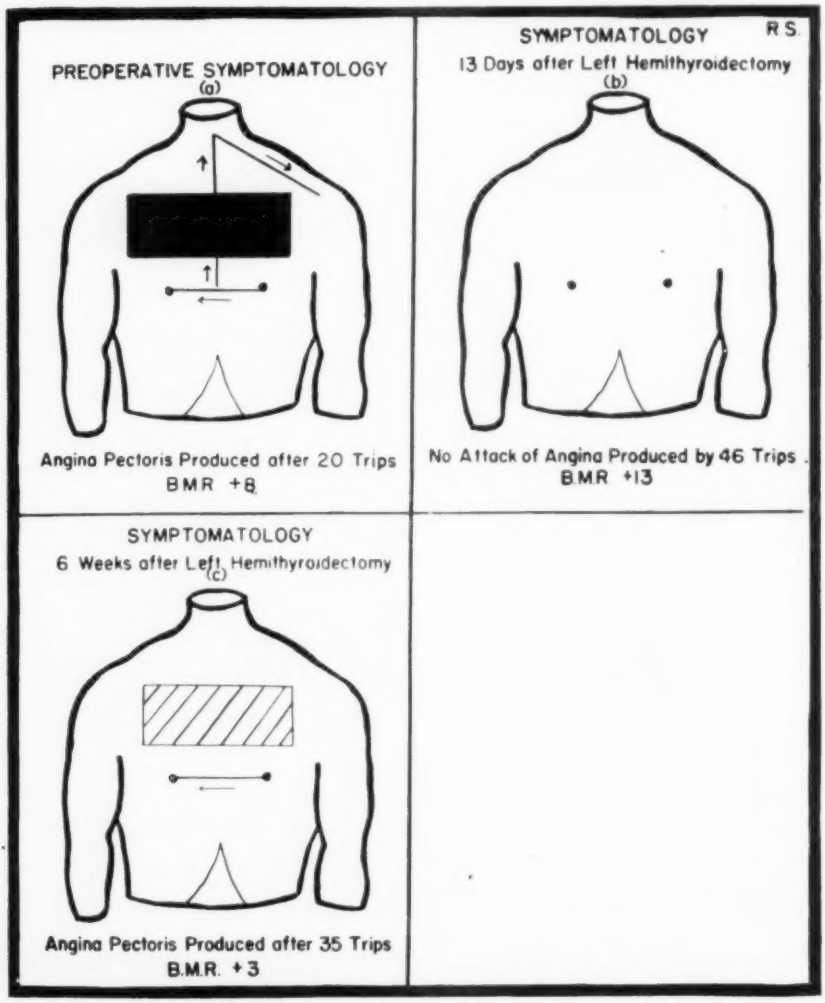

FIG. 6.—Case 20. After left hemithyroidectomy, complete loss of angina pectoris, with partial return of symptoms 6 weeks after operation. Lines indicate radiation of pain; blackened areas indicate oppression; hatched areas indicate diminution in oppression.

chest or arm. At no time before or after operation could satisfactory basal metabolic readings be obtained, in spite of many determinations.

During the 3d postoperative week the pain referable to the left chest gradually returned when attacks occurred spontaneously or under standard conditions. (Fig. 5, *c*.) The sense of oppression was less intense. At the beginning of the 4th postoperative week, the right lobe of the thyroid was completely removed. Ten days after the second lobe of the thyroid had been removed, attacks of angina pectoris were produced on exercise (34 trips on the staircase), pain being experienced over both chests, anteriorly and posteriorly, accompanied by numbness and pain in both arms. (Fig. 5, *d*.) The "heavy, choking and gripping feeling" in the throat was absent, however.

CASE 20.—(*Same as Case 17.*) *Coronary thrombosis, angina pectoris. Loss of angina pectoris after left hemithyroidectomy. Return of symptoms in 6 weeks.* R. S., a male, aged 41, who was admitted with the diagnoses of mitral stenosis and regurgitation, aortic insufficiency, coronary thrombosis and angina pectoris, had attacks of angina which were precipitated by slight exertion but occasionally awakened him at night. The attacks were characterized by "crushing" pain under the xyphoid, with "choking" sensations in the neck and radiation of pain to the left shoulder, left back, left arm and occasionally to the right arm. A "bandlike" sense of constriction in the right and left 3d interspaces was always present during the attacks. In addition to these attacks, he had suffered from a continuous sense of "pressure and stabbing pain" over the precordium, which was aggravated by eating, going to stool, or excitement. These attacks could be precipitated by exercise in the cold (20 trips on the staircase). The distribution of pain at this time is illustrated by Fig. 6, *a*.

The left lobe of the thyroid was completely removed, November 28, 1933, under local novocain anesthesia. Two hours after operation the sense of "tightness" across the left chest had disappeared, as had the sharp "stabbing" pains about the left nipple. Ten hours postoperatively the findings were corroborated, no sedation having been given in the meantime. Thirteen days after operation, on exercise under standard conditions (46 trips), no attack of angina was produced. (Fig. 6, *b*.) The basal metabolic rate was +13%.

Six weeks after left hemithyroidectomy, after 35 trips on the staircase, a mild attack of angina was experienced. (Fig. 6, *c*.)

In brief, after hemithyroidectomy, attacks of angina pectoris pain were not experienced over the side of the chest corresponding to that on which the thyroid had been removed. In 2 patients, M. H. and S. F., attacks of angina pectoris were precipitated as readily as before operation, the pain being confined to the half of the thorax corresponding to the intact lobe of the thyroid. All patients showed immediate postoperative relief on the operated side of non-anginal precordial pain which had been continuously present before operation. The basal metabolic rate showed no lowering after hemithyroidectomy, and within 3 to 6 weeks pain was again experienced as before operation.

The data in this communication on the immediate postoperative relief of pain are representative of a larger series of similar observations.

Discussion. *The early relief of chest pain after complete removal of the thyroid is due to interruption of nerve impulses and is temporary.*

We believe that the foregoing observations constitute convincing evidence that the early relief of pain after total ablation of the thyroid is due to the interruption of nerve pathways bearing afferent impulses from the heart to the central nervous system. This evidence may be summarized as follows:

1. *The loss of hyperesthesia and hyperalgesia of the chest and the subjective relief of precordial pain occurred immediately after operation.* After operations under local novocain anesthesia, the patients were examined and questioned within a few hours. The immediate loss of precordial pain and the sudden disappearance of certain localized areas of hyperesthesia and hyperalgesia could not have been due to diminished circulating thyroid principle within the body, for, even a week after operation, the basal metabolic rate often was only slightly lowered. The immediate postoperative relief was not due to local novocain infiltration for similar findings were observed in patients after general nitrous oxide anesthesia.

2. *The areas of hyperesthesia and hyperalgesia and precordial pain not infrequently reappeared before any considerable reduction in the metabolic rate occurred.* Recurrence of precordial pain occurred at various time intervals and was either partial or complete in intensity. The areas of hyperesthesia and hyperalgesia usually recurred in 3 to 6 weeks. The recurrence of symptoms presumably was due to resumption of function of nerves temporarily rendered nonconductive, to regeneration of nerves, or to other nerves taking over the function of the severed ones. Painful afferent nerve impulses from one source may not be appreciated because of greater cord stimulation from another source, such as the operative incision, the sensation from the latter source taking precedence over the former.[52] This counterirritant mechanism of relief of pain does not apply to our cases, for, although the operative incision was bilateral, the relief of pain was limited to the side on which hemithyroidectomy was performed. Moreover, the relief of pain frequently continued after the operative wound had healed.

3. *The unilateral relief of pain, typical of angina pectoris, by hemithyroidectomy constitutes striking evidence of the interruption of afferent impulses from the heart.* In each of the 3 patients with bilateral distribution of anginal pain, the attacks were not experienced over the side of the chest corresponding to that on which the thyroid had been removed. The characteristics of the attacks of angina pectoris, so far as they were referred to the unoperated side of the chest, were usually uninfluenced by operation. These findings in the 3 patients who had complete removal of only 1 lobe of the thyroid are plainly inconsistent with possible theories based on generalized changes of a metabolic or endocrine nature.

4. *The early relief of pain after thyroidectomy is closely analogous to the early effects of cervical sympathectomy.* Both hemithyroidectomy and unilateral cervical sympathectomy are attended by

somewhat irregular therapeutic effects. The relief is usually confined to the side of operation; recurrence of symptoms may be partial or complete and not infrequently occurs after an interval of days or weeks. Other changes were noted following thyroidectomy which indicate sympathetic nerve injury or stimulation; dilatation of 1 pupil was present for several days after operation in 2 patients; in 3 others, paresthesias of the neck, head and chest occurred, lasting 1 to 3 weeks. We have observed, moreover, that injection of the stellate ganglion with novocain causes temporary relief of hyperesthesia and hyperalgesia on the homolateral side of the chest.

The present status of knowledge regarding the anatomy and pathologic physiology of the cervical sympathetic nerves does not permit us to state the exact pathways that suffer interruption. "Viscerosensory" or "visceromotor reflex arcs" may be affected.[35] Impulses from the heart reach the central nervous system directly through the thoracic sensory nerves and also by way of sensory fibers traveling the same pathway as the cervical sympathetic fibers.[34] The relative importance of these 2 routes evidently varies from person to person, thereby accounting for the great variability in therapeutic results of cervical sympathectomy as well as the variability of the early relief of pain found by us following thyroidectomy in different individuals. Complete surgical removal of the thyroid probably does not involve severance of the main cervical sympathetic trunk or ganglia or of the cardiac nerves in the neck, although some of the numerous ramifications of this system, such as the plexuses along the inferior and superior thyroid arteries, may suffer interruption.

The early relief of pain is not due to decrease in sensitivity of the heart to epinephrin or other endocrine substances. As pointed out in a previous communication,[12] the heart in patients with angina pectoris may be less sensitive to epinephrin when the basal metabolic rate is lowered following total thyroidectomy. This assumption is based on experimental observations that the effect of epinephrin on the heart may be enhanced in man and animals receiving thyroid active principle, and, conversely, may be diminished in patients with myxedema.[1, 15, 21, 32, 36, 42] These findings, based on blood pressure and heart rate measurements, have received clinical application in the "Goetsch test."[24] Experience has shown, however, that the sensitivity of the heart to epinephrin is far too irregular both in normal man and in patients with thyroid disease to be an index of the degree of thyroid activity.[14, 46, 51]

The early relief of pain following thyroidectomy, as described above, is not associated with a significant reduction in the amount of circulating thyroid active principle. That the relief in these patients during this period can be due neither to reduction in the basal metabolic rate nor to decreased sensitivity of the heart to epinephrin is, therefore, obvious. Our own observations of the effect of epinephrin in such patients are in accord with this con-

sideration. This concept is further substantiated by the fact that patients in whom hemithyroidectomy was performed experienced unilateral relief of pain on the operated side. Mechanisms based on early general metabolic or endocrine influences, moreover, cannot explain the temporary return of precordial pain which frequently occurs several weeks after total ablation of the thyroid, and before the basal metabolic rate has dropped appreciably.

The permanent relief of pain occurs later in the postoperative course with the development of the hypothyroid state as gauged by the basal metabolic rate. The foregoing observations reaffirm the importance of the lessened work of the heart, when the metabolic rate becomes lowered, as the basis for permanent improvement in patients with angina pectoris or congestive failure. Earlier measurements of the velocity of blood flow in various clinical conditions indicated that the work of the heart was greatly decreased in myxedema and that a damaged heart, while unable to supply the demands of the body at normal metabolic rates, might nevertheless be able to supply the lowered tissue demands after complete thyroidectomy.[8] In accord with these considerations we have found that the signs of circulatory insufficiency lessen most markedly as the amount of circulating thyroid principle, as gauged by the metabolic rate, diminishes, and that the degree of permanent improvement in patients with congestive failure or angina pectoris is closely related to the extent of the lowering in the basal metabolic rate. As Means stated, 1924, in his monograph on dyspnea, "First of all comes treatment directed toward reduction of the metabolic rate. This is seen most strikingly in treatment by rest, particularly in heart failure."[37] In patients with low pre-operative basal metabolic rates, the improvement has not been as striking as in patients with normal pre-operative metabolic rates in whom the postoperative decrease was greater.

According to current knowledge, the outstanding function of the thyroid is to regulate the general level of metabolic activity, with important effects also on the nervous system and on growth.[39] The chief expenditures of cardiac energy are in relation to cardiac output and velocity, ventricular rate and blood pressure.[5, 10] Studies on which we are engaged indicate that these various factors all play a part, but that the reduction in the cardiac output and velocity is most important in releasing the heart from strain; the reduction in ventricular rate is of secondary importance and changes in the blood pressure are negligible.

Changes in supply and demand also contribute to the benefits conferred to patients with angina pectoris.[7–10, 38] At rest, the coronary circulation is evidently adequate to the needs of the heart muscle, as evidenced by freedom from pain. During exercise, however, as a result of organic lesions such as arteriosclerotic narrowing of the coronary vessels, the coronary blood supply cannot increase in accord with the increased needs of the heart, and so pain ensues.[28, 38, 49]

Following permanent reduction in the basal metabolic rate by thyroidectomy, there is marked reduction in the work demanded of the heart, as gauged by the velocity of blood flow and cardiac output.[4, 10, 13] During exercise the demands of the heart for oxygen and nutrition rise. Since the heart in the hypothyroid state is starting at a lower level of oxygen consumption than in the normal state, it can withstand a greater increment of work before reaching the upper limit of oxygen supply set by the relatively fixed coronary vessels. The rôle of this factor is being investigated.

Another benefit conferred by thyroidectomy on the hearts of patients with chronic heart disease may be the total decreased expenditure of cardiac energy associated with the lowered total metabolism of hypothyroidism.[20] The value of bed rest in patients with angina pectoris has long been recognized by clinicians. The reduction in total metabolism toward the basal rate which accompanies bed rest greatly diminishes the work of the heart[20] and is associated with clinical improvement. This is in accord with the findings of other observers that conditions which increase the work of the heart precipitate attacks of angina[16–18, 45, 48] and, conversely, that treatment which reduces the burden on the heart alleviates angina pectoris.[2, 25, 26, 31]

Our experience has been in accord with these considerations. Of 20 patients with angina pectoris, all operated upon without mortality, 14 have been able to undertake various degrees of work; 4 are recently postoperative; the 2 who received only slight relief had low basal metabolic rates prior to operation and consequently showed no great further reduction before thyroid extract had to be administered to prevent myxedema.

The relation between the early relief of pain due to nerve impulse interruption and the later permanent relief of pain due to lowering of the metabolic rate. According to current concepts, there are 3 ways in which referred visceral pain may be abolished: (1) Abolition of cutaneous afferent impulses; (2) interruption of the nerves carrying abnormally strong visceral afferent impulses; (3) altering the state of the viscus so that it no longer gives rise to abnormally strong impulses. The 1st mechanism, studied extensively in various diseases by Weiss and Davis,[53] plays no rôle in the relief of pain after thyroidectomy. The cutaneous nerves of the areas studied are not affected, for anesthesia of the skin was not demonstrable in our subjects, in contradistinction to the observations after novocain infiltration of Weiss and Davis. In patients with hemithyroidectomy, unilateral relief was experienced, although the skin incision was the same as for total thyroidectomy. The 2d mechanism is probably the basis of the early relief of pain experienced by our patients and may have either an anatomic or a physiologic basis. In some patients, practically all afferent impulses may be interrupted; in others a sufficient number of impulses may be blocked so that the remaining functioning fibers transmit stimuli which are only sub-

liminal. The 3d mechanism provides the later and permanent relief of pain by permanent reduction in the basal metabolic rate and the lessened demands on the heart.

It should be noted that the 2 mechanisms which we regard as providing relief of pain are independent in their action and occur at different times postoperatively.

After total thyroidectomy, in some patients the metabolic rate became lower while the early relief of pain was present. In these patients, therefore, the relief of pain was continuous. (Fig. 7, *c*.) In other patients, however, the pain due to nerve impulse interruption recurred, only to disappear permanently when the basal metabolic rate showed a marked reduction. (Fig. 7, *b*.) In other patients there may be no early relief of pain. (Fig. 7, *a*.) Obviously various combinations of these two variable mechanisms produce a variable clinical course in any given patient.

The observation of unilateral relief of pain after hemithyroidectomy raises considerations of practical importance. The underlying pathologic disorder was evidently unaffected, for the attacks of anginal pain on the other side of the chest were usually precipitated as readily and as intensely as previously. The abrupt cessation of attacks sometimes witnessed immediately after bilateral removal of the gland may, therefore, be due to interruption of impulses from the heart to the central nervous system without reflecting any fundamental improvement in the heart itself. The unilateral relief of angina pectoris immediately after hemithyroidectomy is strong evidence that early bilateral relief after total thyroidectomy is due to the same mechanism. Such patients may simply be unaware of attacks during their early convalescence after total ablation of the thyroid and, by undertaking exertion too soon, may jeopardize their well-being. The advisability of enforcing complete bed rest in such patients, as well as in all others, until the basal metabolic rate shows significant lowering is apparent.

Summary and Conclusions. 1. Observations on the immediate postoperative relief of chest pain after total thyroidectomy in 19 patients are described.

2. Data were collected before, immediately after and during several weeks after operation in 3 groups: (1) Changes in non-anginal precordial pain; (2) changes in areas of skin hyperesthesia and muscle and periosteal hyperalgesia of the chest wall; (3) changes in the character and distribution of pain of angina pectoris.

3. Within a few hours after operation, non-anginal precordial pain, hyperalgesia and hyperesthesia disappeared, remained absent for 2 to 4 weeks, but then usually reappeared if the basal metabolic rate had not declined significantly. Only after the basal metabolic rate had dropped appreciably did the above-mentioned signs and symptoms diminish or disappear permanently.

4. Studies were made on the distribution of the pain of angina pectoris produced under standard conditions in 3 patients before

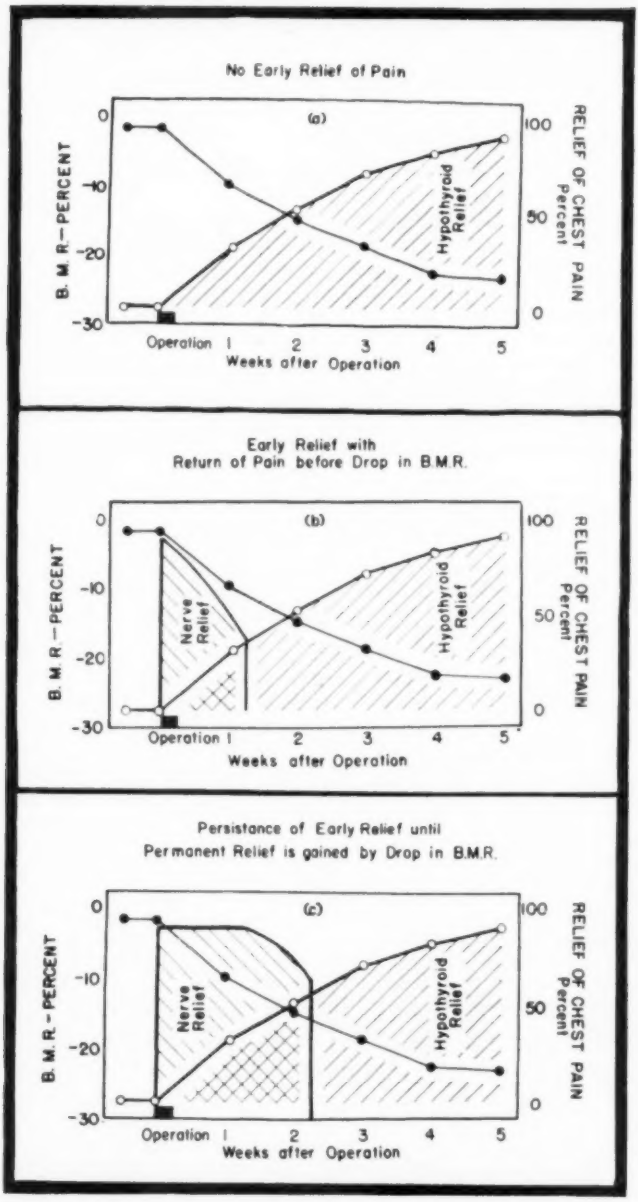

FIG. 7.—Possible variations in the clinical picture of relief of chest pain and angina pectoris following total thyroidectomy. The hatched area, on the left of chart, bounded by the solid black line indicates early relief of pain due to nerve injury; the hatched area, on the right of the chart, bounded by the line broken by circles indicates the development of permanent relief of pain due to the development of the hypothyroid state. The cross-hatched area indicates overlapping of these two mechanisms. The basal metabolic rate lines represent actual average values taken from the postoperative course of 25 patients after total ablation of the thyroid. The curve after subtotal thyroidectomy in patients with toxic goiter is somewhat different according to the work of Segall and Means.[47]

and after hemithyroidectomy. The remaining half of the thyroid gland was removed at a later date. Exercise within 2 weeks after hemithyroidectomy produced no pain in the arm and the side of the chest corresponding to the side of operation. The pain of angina pectoris was experienced only on the unoperated side and usually stopped sharply at the midline of the sternum. The similarity of these findings to those after cervical sympathectomy and alcohol injection is discussed. The basal metabolic rate did not change appreciably after the 1st hemithyroidectomy. After 2 to 8 weeks, pain on exercise was again experienced on the operated side. Only after removal of the other $\frac{1}{2}$ of the thyroid gland and after an appreciable drop in the basal metabolic rate was the pain of angina pectoris permanently relieved.

5. These observations point definitely to the following conclusions: (1) The immediate relief of pain after total thyroidectomy is due to the interruption of afferent nerve impulses from the heart at the time of operation; (2) relief by this mechanism is only temporary; (3) permanent relief is related to the lessened work of the heart attendant on the development of the hypothyroid state.

6. These findings indicate that, after total ablation of the thyroid, complete bed rest should be enforced, despite the early subjective relief experienced by the patient, until the basal metabolic rate shows significant lowering.

We wish to thank Dr. James C. White for his helpful suggestions.

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RHEUMATIC HEART DISEASE: CLINICAL DATA AS OBSERVED IN LOUISVILLE, KENTUCKY.*

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In the present study a 5-year survey of rheumatic heart disease in a charity hospital in Kentucky (L. C. H.) is offered. The purpose of this investigation is to ascertain the incidence and course of

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rheumatic heart disease in this section and to compare the data in this group of cases with similar groups reported in the literature from other sections of the United States.

There were admitted to the wards of this hospital during the 5-year period of this study (1928–1933) 206 proven cases of rheumatic heart disease being 8% of the total admission of cardiac cases.

Race and Sex. In this group there were 84 males (41%) and 122 females (59%). This shows the usual more frequent incidence of the rheumatic infection in females in the ratio of 3 to 2. The racial incidence was 130 whites (63%) and 76 colored (37%) (Table 1).

TABLE 1.—RACE AND SEX INCIDENCE (COMPLETE GROUP).

	Sex			Race	
	Cases.	%		Cases.	%
Males	84	41	White	130	63
Females	122	59	Colored	76	37
Total	206	100	Total	206	100

Etiology. Of this series 140 cases (68%) gave a definite history of mild or severe rheumatic fever; 40 (19.4%) had only recurrent attacks of tonsillitis; and 9 (4.3%) gave a history of chorea. Seventeen (8.2%) gave no history of previous illness that could be interpreted as a rheumatic infection. The sexes were almost equal in the chorea group and were in the ratio of 2 to 3 in the rheumatic fever and tonsillitis group (Table 2).

TABLE 2.—ETIOLOGY OF COMPLETE GROUP.

			Sex	
	Cases.	%	Males.	Females.
Rheumatic fever	140	68.0	55	85
Chorea	9	4.3	4	5
Tonsillitis	40	19.4	13	27
No history	17	8.2	7	10
Total	206	100.0	79	127

In the group of 140 cases giving a history of rheumatic fever, it is interesting that only 2 developed the infection before 5 years of age. The first rheumatic attack was before the age of 20 in 98 cases (70%) and 131 (93.5%) were stricken before the age of 30.

TABLE 3.—THE INCIDENCE OF RHEUMATIC FEVER BY DECADES.

Decades.	Cases.	%
0 to 10 years	28	20.0
10 to 20 years	70	50.0
20 to 30 years	33	23.5
30 to 40 years	8	5.7
40 to 50 years	1	0.8

Onset of Symptoms. At some time during the 5-year period covered by this study 155 cases of the whole group were admitted

with cardiac symptoms (Table 4). There was a progressive increase in the number showing symptoms with each decade to the age of 40. The greatest number showed cardiac symptoms between the second and fifth decades (58%). Nine cases did not develop symptoms until after the 50th year. Fifty-one cases were in the hospital for other conditions and signs of rheumatic heart disease were unexpectedly discovered.

TABLE 4.— ONSET OF CARDIAC SYMPTOMS (155 CASES).

Decade.	Cases.	%
0 to 10	6	4
10 to 20	35	22
20 to 30	40	26
30 to 40	50	32
40 to 50	15	10
50 or over	9	6
Total	155	100

Clinical Diagnosis. The whole group classified according to the clinical diagnosis of valvular involvement shows: (1) Mitral, 160 cases; (2) aortic, 11 cases; (3) mitral and aortic, 22 cases, and (4) auricular fibrillation, 13 cases. In 21 cases of the group a diagnosis of mitral stenosis and auricular fibrillation was made clinically. Therefore, in the entire group auricular fibrillation was present clinically in 34 cases. Mitral valve involvement alone was present in 83%, aortic lesions alone in 5.7% and both mitral and aortic involvement in 11.3%.

TABLE 5.—CLINICAL DIAGNOSIS OF VALVULAR LESIONS (193 CASES).

Valve.	Cases.	%
Mitral	160	83.0
Aortic	11	5.7
Aortic and mitral	22	11.3
Total	193	100.0

Deaths. To permit comparative study, the cases in which death occurred in the hospital have been divided into two groups: (1) fatal cases not autopsied, 25; and (2) fatal cases autopsied, 11.

Discussion. GROUP 1. (Fatal cases without autopsy.) This group is comprised of 25 cases and shows a definite dominance of females, 11 members of the group being males and 14 females, a ratio of 4 to 5 (Table 6). Sixteen cases gave a history of rheumatic fever, 7 gave a history of tonsillitis, and 2 no history of a rheumatic infection. The initial attack of rheumatic fever occurred before the 30th year in every case except one (96%). The greatest incidence occurred in the 2d decade, 9 cases (56%). The greatest number of this group had onset of cardiac symptoms in the 3d decade of life, and in only 3 cases were symptoms delayed until after 50. Mitral stenosis was diagnosed in 12 cases, mitral and aortic lesions in 5, mitral stenosis and auricular fibrillation in 5, and auricu-

TABLE 6.—FATAL CASES (NO AUTOPSY).

Case No.	Age.	Sex. Male.	Sex. Female.	Rheu. fever.	Tonsillitis.	Chorea.	Age.	Onset of symptoms.	Death.	Valve lesion.	Cause of death (clinical).
1	22		F.	+			22	32	32	Mitral	Congestive failure.
2	19		F.		+		21	24		Aur. fibrillation	Congestive failure.
3*	34		F.					32	34	Aur. fibrillation	Congestive failure.
4	24	M.		+			15	24	25	Mitral.	Congestive failure.
5	40		F.		+			40	40	Mitral	Congestive failure.
6	32		F.	+			10	31	33	Mitral	Congestive failure.
7	33	M.			+			21	33	Mitral	Sub. bacterial endocarditis.
8	51		F.		+			50	51	Mitral	Pericardial effusion.
9	44		F.	+			23	42	48	Mitral; aur. fibrillation	Congestive failure.
10	49		F.	+			6	47	49	Mitral; aur. fibrillation	Congestive failure.
11	46		F.	+			35	46	46	Mitral	Congestive failure.
12	37		F.		+			33	37	Mitral; aur. fibrillation	Congestive failure.
13	55	M.		+			17	52	55	Mitral	Congestive failure.
14*	22	M.						20	22	Mitral; aur. fibrillation	Congestive failure.
15	45		F.	+			10	32	35	Mitral	Congestive failure.
16	31	M.		+			20	31	31	Mitral and aortic	Congestive failure.
17	32		F.	+			28	31	34	Aur. fibrillation	Congestive failure.
18	31	M.			+			30	31	Mitral and aortic	Congestive failure.
19	32	M.		+			20	30	32	Mitral and aortic	Pneumonia.
20	37	M.		+			24	24	37	Mitral	Congestive failure.
21	52	M.		+			12	52	52	Mitral and aortic	Congestive failure.
22	44	M.			+			35	44	Mitral; aur. fibrillation	Congestive failure.
23	26		F.	+			12	22	29	Mitral	Congestive failure.
24	42		F.	+			18	34	45	Mitral and aortic	Congestive failure.
25	31	M.		+			14	31	31	Mitral	Congestive failure.
Totals and average		11	14	16	7	0	18	34	38	25	25

* No history of rheumatic infection.

TABLE 7.—FATAL CASES (AUTOPSIED).

Case No.	Age.	Sex. Male.	Sex. Female.	Rheu. fever.	Tonsillitis.	Chorea.	Age.	Onset of symptoms.	Death.	Cause of death.
1	22	M.			+			2	21	Mitral stenosis. Positive blood culture. Followed scarlet fever. Death due to septicemia.
2	39		F.	+			16		39	Mitral stenosis. No symptoms. Death due to ruptured uterus.
3	51		F.	+			24	51	53	Mitral stenosis. Infarct left lung. Coronary sclerosis. Congestive failure.
4	31	M.		+			14	31	31	Vegetative endocarditis. Mitral stenosis. Congestive failure.
5	36	M.		+			36	36	36	Aortic and mitral stenosis. Postoperative death from ruptured duodenal ulcer.
6	18		F.	+			13	17	19	Mitral steonosis. Congestive failure.
7*	42		F.					42	42	Generalized valvulitis. Congestive failure. All valves incompetent.
8	45		F.			+	6	26	27	Mitral stenosis. Infarct both lungs. Congestive failure.
9*	40	M.						39	40	Mitral stenosis. Coronary sclerosis. Congestive failure.
10*	19	M.						19	19	Mitral stenosis. Vegetative endocarditis. Congestive failure.
11	10	M.		+			9	11	13	Mitral stenosis. Congestive failure.
Totals and averages	32	6	5	6	1	1	17	27	30	

* No history of rheumatic infection.

lar fibrillation alone in 3 cases. The average age at death in the whole group was 38 years. The average age at death in the cases of pure mitral stenosis was 35; in the cases of mitral and aortic lesions, 38; mitral stenosis and auricular fibrillation, 40; and in the cases showing only auricular fibrillation the average age at death was 30 years. The cause of death based on clinical diagnosis was congestive failure in 22 cases (88%). Subacute bacterial endocarditis, pneumonia, and pericarditis with effusion were responsible for 1 death each.

Group 2. (Deaths, autopsied.) This group is comprised of 11 cases, 6 males and 5 females. As to etiology, 6 cases gave a history of rheumatic fever, 1 a history of tonsillitis, 1 had chorea and 3 gave no history of rheumatic infection. The average time elapsing from the first attack of rheumatic infection to the onset of symptoms was 10 years. The average time from onset of symptoms to death was 3 years. The cause of death was congestive failure in 8 cases. One died from a ruptured uterus, 1 from septicemia following scarlet fever, and 1 from a ruptured duodenal ulcer (postoperative). Nine cases of this group showed mitral stenosis, 1 showed both aortic and mitral stenosis and in 1 all valves were incompetent.

Comparison of Findings with Other Sections of the United States. It is interesting to note the incidence of rheumatic heart disease in the Louisville City Hospital is practically the same as reported from Texas by Stone and Vanzant (1927), and is in close agreement with statistics submitted by Harrison and Levine (1924) from a charity hospital in New Orleans. It serves to emphasize the effect of climate in the incidence of the rheumatic state. This study would indicate that, in general, White's conclusions with reference to this point may be accepted. In other words, in the southern United States the rheumatic infection occurs about $\frac{1}{4}$ as often as in New England and about $\frac{1}{2}$ as often as in Virginia and Maryland. Throughout, the infection is essentially one of youth and early adult life. In general, the infection behaves the same in all latitudes, producing the same characteristic endocardial lesions, and possibly invading the walls of the larger bloodvessels with resulting fibrosis and scars. The predominating lesion in groups reported from different communities is mitral stenosis. The victims generally must lead sheltered lives and death overtakes them in the third and fourth decades of life. The most usual cause of death is congestive failure in all series reported from that standpoint.

Summary. In this study of 206 cases of rheumatic heart disease seen in the Louisville City Hospital, it was revealed that 84% were less than 50 years of age. The disease occurred most commonly in the 3d and 4th decades of life (58%). Only 9 patients (6%) were more than 50. The sex incidence showed the usual greater frequency of the infection in females in the ratio of 3 to 2. There was a predominance of white patients to colored in the ratio of 5 to 3. There

was a definite history of rheumatic infection in 189 cases (91%). One hundred and forty cases (68%) had rheumatic fever. The first attack occurred before the age of 30 years in 131 cases (93.5%) and before the age of 20 in 98 cases (70%). The primary infection occurred in only 1 case after the age of 40.

One hundred and fifty-five cases were in the hospital some time during the period covered by this study with cardiac symptoms (75%). The greatest number developed symptoms during the 3d and 4th decades of life, and 131 cases (85%) had shown some degree of decompensation before the 40th year. Only 9 cases were over 50 when symptoms appeared.

For the purpose of comparative study the fatal cases in this series were divided into two groups according to autopsy or no autopsy examination. Group 1, in which no autopsy examination was made, comprised 25 cases, and Group 2, in which an autopsy examination was made; 11 cases. In Group 1, 11 patients were males and 14 were females; the rheumatic infection occurred before the 30th year in every case except 1. The average age at death was 36 years. In Group 2 there were 6 males and 5 females; the rheumatic infection occurred before the 30th year in every case except 1; and the average age at death was 30 years. At autopsy 9 cases showed mitral stenosis, 1 mitral and aortic stenosis, and 1 showed incompetency of all valves. Death was due to congestive failure in 30 of the 36 fatal cases. One died of a ruptured uterus, 1 of a ruptured duodenal ulcer (postoperative), 1 of septicemia, 1 of pneumonia, 1 of pericarditis with effusion, and 1 of subacute bacterial endocarditis.

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THE CLINICAL SIGNIFICANCE OF LOW T-WAVES IN THE ELECTROCARDIOGRAM.

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Although the clinical significance of inverted *T*-waves in one or more leads of the electrocardiogram has been studied extensively, little information is available concerning upright *T*-waves of small amplitude. In 1924, Pardee[1] stated that a *T*-wave less than 2 mm.

in amplitude in the lead showing the largest excursion should probably be considered abnormal. Master[2] believes that low voltage *T*-waves not exceeding 1 mm. amplitude in any lead furnish significant evidence of cardiac damage. The present study is concerned with *T*-waves less than 2 mm. in amplitude in Leads I and/or II. The electrocardiograms have been classified as follows: (A) Low *T*-wave in Lead I and normal *T*-wave in Lead II. (B) Low *T*-waves in Leads I and II and either low or slightly inverted *T*-wave in Lead III. (C) Normal *T*-wave in Lead I, low or flat *T*-wave in Lead II and inverted *T*-wave in Lead III.

Some of the tracings of Type B are similar to those published by Master, although in many the *T*-waves are greater than 1 mm. in amplitude, in one or more leads.

The clinical material used in the study has been divided into the following groups:

(1) 709 college students with presumably normal cardiovascular systems; (2) 23 cases having a "vertical" heart; (3) 25 pregnant women; (4) 202 cases showing a low *T*-wave (less than 2 mm.) in Lead I or II or both; (5) 100 cases with normal electrocardiograms; (6) 143 cases with hypertension; (7) 145 railroad executives.

Group I. The records of 709 college students with presumably normal cardiovascular systems were made available by Dr. Francis C. Wood. There were 46 cases whose *T*-waves conformed to one or another of the types under consideration; 34 to Type A; 7 to Type B, and 5 to Type C.

Analysis of the records showing a low *T*-1 suggested a relationship between this wave and the *Q-R-S* complex of Lead I. In 32 the amplitude of the *Q-R-S* complexes was 6 mm.* or less and in 23, 4 mm. or less. It would, therefore, appear that in young individuals with apparently normal hearts, a low *T*-wave in Lead I is encountered in less than 5% of the cases and in most of these the *Q-R-S* complex is also of low amplitude. However, the converse is not true, for *T*-waves of normal amplitude are frequently found associated in Lead I with low *Q-R-S* complexes.

Orthodiagrams were available in only 9 of the 32 cases showing a low *T*-1, but it was noteworthy that 7 of the 9 showed a "vertical" heart.

Examination of the 7 records with a low *T*-1 and *T*-2 showed *Q-R-S*-1 complexes of less than 6 mm. in 4 instances. Orthodiagrams were available in 3 of the 4 cases showing a low *Q-R-S*-1, and in 2 the heart was of the vertical type. The *Q-R-S* complexes of the remaining 3 cases were split or slurred in all leads. Follow-up studies of these individuals have not been obtained and the significance of the finding is not known.

Further examination of the 5 electrocardiograms showing a normal *T*-1, low *T*-2 and inverted *T*-3 revealed nothing else of note. Ortho-

* Throughout this paper an *R*-1 of 6 mm. amplitude or less will be considered as low.

diagrams were available in 3 cases and in each the left diaphragm was on the level of the right; in 2 cases the heart appeared transversely placed.

GROUP II. The frequency of vertical hearts in young individuals with low *T*-1 waves suggested that position of the heart may be an important factor in producing the low *T*-1. Low *Q-R-S* complexes in Lead I have frequently been noted in electrocardiograms of patients whose hearts were of the vertical type,[1] and, as is well known, in cases with a tendency toward right axis deviation, particularly mitral stenosis. In order to obtain some idea regarding the frequency of low *T*-1 waves in cases with vertical hearts, a group of orthodiagrams exhibiting such hearts was selected at random from the orthodiagraphic files. Only those orthodiagrams exhibiting a normal-sized heart were chosen; records suggesting a "mitralized" heart were not included. The clinical histories and electrocardiograms of these cases were then studied and those with evident cardiovascular disease excluded. Twenty-three cases remained and in 17 the *R*-waves in Lead I were 6 mm. or less in amplitude; in 7 records, *T*-1 was less than 2 mm. A low *T*-1 was associated with a low *R*-1 in 6 cases. It would therefore appear that in patients with vertical hearts, a low *Q-R-S* complex is obtained in the majority in Lead I. Furthermore, the low *Q-R-S* complex frequently has associated with it a low *T*-1.

GROUP III. The position of the heart also affects the *T*-waves in Leads II and III. Bland and White[3] have noted a complete inversion of Lead III in transversely placed hearts and Proger[4] has shown that *T*-3 is inverted in a large percentage of obese individuals with apparently normal hearts. In order to study the influence of a high diaphragm upon *T*-3, the electrocardiograms of 25 pregnant women (9th month) were examined. In 22, *T*-3 was inverted, in 2 it was flat and in only 1 was it upright. Although there are factors other than a high diaphragm which may influence the form of the electrocardiogram during pregnancy, it was noteworthy that in 10 cases examined after delivery, *T*-3 which had been inverted became upright or flat in 9 and in only 1 was there no change. Although the *T*-wave in Lead II was of low amplitude in only 3 of the 25 cases, in each of these 3 cases *T*-3 was inverted; following delivery, *T*-2 became of normal amplitude and *T*-3 upright. In all cases the *T*-wave in Lead I was of normal amplitude and in 13 cases 4 mm. or more. Of the 10 cases examined after delivery, 9 showed a reduction in amplitude of *T*-1; although this reduction was slight in some cases, nevertheless in 4 instances it was 2 mm. or more.

GROUP IV. In order to correlate the clinical and electrocardiographic findings in cases whose electrocardiograms showed a low *T*-wave in one or more leads the records of 202 clinic and ward patients were studied. This group was divided as follows:

Type A, 68 cases; Type B, 80; Type C, 54.

A. Among these 68 cases, the clinical records disclosed cardiovascular abnormalities in 57 (83.8%); 3 cases (4.4%) were considered doubtful because their complaints or findings pointed to cardiac damage but sufficient evidence was not found to warrant a definite diagnosis; in 8 (11.8%) there was no evidence of cardiovascular abnormality. Although 22 tracings showed a low *R*-1, in 5 cases there was mitral stenosis and right axis deviation; in 2, mitral stenosis without right axis deviation. In only 2 instances was there a vertical heart without evidence of organic disease.* All of the remaining 13 cases showed some cardiac abnormality. The association of low *T*-1 and *R*-1, as found in Groups I and IV, therefore, may be due either to vertical position of the heart or to myocardial change, the incidence of each depending on the type of clinical material being studied.

The clinical diagnosis of those cases showing a cardiovascular abnormality are as follows: Hypertension and/or arteriosclerosis (including 3 cases of angina pectoris), 23; rheumatic heart disease, 10; myocardial disease (etiology unknown), 7; thyrotoxicosis, 6; syphilitic heart disease, 5; miscellaneous, 6.†

B. In this group there were 80 cases. The clinical records of 70 (87.5%) disclosed cardiovascular abnormalities; in 2 (2.5%) the diagnosis was doubtful, and 8 (10%) were negative. The clinical diagnoses of the positive cases are: Hypertension and/or arteriosclerosis (including 2 cases of angina pectoris), 24; rheumatic heart disease, 12; myocardial disease (etiology unknown), 14; thyrotoxicosis, 10; syphilitic heart disease, 5; miscellaneous, 5.

C. In this group there were 54 cases and, of these, 34 (63%) disclosed cardiovascular abnormalities, 2 (3.7%) were doubtful, and 18 (33.3%) were negative. The clinical diagnoses of those cases considered positive are: hypertension and/or arteriosclerosis, 13; rheumatic heart disease, 6; myocardial disease (etiology unknown), 3; thyrotoxicosis, 5; syphilitic heart disease, 4; miscellaneous, 3.

The chief significant difference elicited among the 3 types appeared to be the somewhat higher percentage of cases with negative or doubtful clinical findings in Type C.‡ It is worthy of note that in 6 of the 20 cases falling in this category (Type C) the heart was transversely tilted by a high diaphragm.

Group V. The clinical histories of 100 ward and clinic patients whose electrocardiograms were considered normal were studied. This group was considered essential as a control group and the

* There were only 2 cases of hypertension in the group of 22 showing a low *R*-1. The association of a normal or large *R*-1 and a low *T*-1 is apparently much more frequent in such cases.

† Under "miscellaneous" are grouped such conditions as congenital heart disease, acute and subacute bacterial endocarditis, acute pericarditis, pleuropericarditis, metastatic carcinoma and severe cases of kyphoscoliosis.

‡ Thirty-two (15.8%) of the 202 cases showed slurring or splintering of the *Q-R-S* complexes in one or more leads; 15 belong to the group considered under Type A, 10 to Type B and 7 to Type C.

cases were chosen at random from electrocardiographic files. Forty-one of this group were considered as having positive evidence of cardiovascular abnormality, 9 were doubtful and 50 were considered negative. The clinical diagnoses of those cases considered positive are: hypertension and/or arteriosclerosis (including 1 case of angina pectoris), 16; rheumatic heart disease, 12; myocardial disease (etiology unknown), 1; thyrotoxicosis, 4; syphilitic heart disease, 5; miscellaneous, 3.

The negative group consisted of a great variety of conditions. Although the patients in this group were derived from the same sources as those of Group IV, the different incidence of cardiovascular disease is striking. This finding points strongly to the significance of low *T*-waves.

Group VI. This group consists of 145 corporation executives. They are of importance in this study because of the frequency of arteriosclerosis and hypertensive cardiovascular disease in this group. All were referred for routine examination and all were on the active list of this corporation at the time of examination although 1 had had a coronary occlusion.

A. There were 20 records with a low *T*-wave in Lead I. Clinically, 10 were considered as having a cardiovascular abnormality. Of the remainder the low *T*-wave was associated with a low *R* in 7 instances; in 5 of these 7 the heart was vertical. It was smaller than normal in 3 of these 5. Of the 3 remaining cases, focal infection (teeth and tonsils) was stressed in the clinical records of 2; the third was considered negative.

B. There were 4 records showing a low *T*-1 and *T*-2. The electrocardiogram of 1, a man of 32, showed a low *R*-1. Clinically nothing but a few abscessed teeth were found. The other 3 disclosed findings indicative of cardiovascular damage.

C. There were 2 cases with a low *T*-2 and inverted *T*-3. One showed a slight increase in width of the aorta on fluoroscopic examination but was otherwise negative. Nothing of significance was found on examination of the other.

Group VII. Because of the great number of cases of hypertension showing a low *T*-wave in important leads (Group IV), a group of 143 cases of hypertension was studied. Only those patients with systolic blood pressure consistently above 150 mm. or diastolic pressure consistently over 100 mm. are included. Master,[5] in his study of hypertensive hearts, found left axis deviation in 74% and left axis deviation with inversion of *T*-1 in 36% of cases. In our group of 143 cases left axis deviation was found in 95 (66.4%); in 59 cases (41.3%) the *T*-wave was diphasic or inverted in Leads I or II or both. In 30 instances (21%) the *T*-waves corresponded to one of the types under consideration in this study, 15 to Type A, 12 to Type B and 3 to Type C. The much greater incidence of these types in hypertension than in normal controls constitutes evidence

of their significance. It is also of interest that only 3 of the group of 30 cases with low *T*-waves showed a low *R*-1.

Discussion. Variations in the angle of the electrical axis of the heart in the normal individual is an important factor in determining the height and form of the components of the electrocardiograms. Although intrathoracic conditions are frequently responsible for changes in the anatomical axis of the normal heart and presumably also of the electrical axis, the position of the diaphragm is probably the most frequent factor.

That a low *T*-wave in Lead I is frequently dependent on a low position of the diaphragm is supported by several observations: (1) The frequency of low *T*-1 in the group of vertical hearts; (2) in tracings taken during inspiration and expiration, *R*-1 and *T*-1 frequently tend to become smaller during inspiration; (3) following pregnancy the *T*-wave in Lead I became smaller in the majority of cases.

The view that a high diaphragm tends toward an inversion of *T*-3 is supported by the following: (1) The frequency of inverted *T*-3 in electrocardiograms of pregnant women and their reversion to an upright *T*-wave after delivery; (2) the frequency of inversion of *T*-3 in obese individuals; (3) the changes in *T*-3 during a deep expiration.

It therefore appears that in properly evaluating the significance of a low *T*-1 or *T*-2 in doubtful cases, cognizance must be taken of the position of the heart; in vertical hearts without evidence of disease, *T*-1 may be low or flat but is usually associated with a low *R*-1, and in obese individuals an inverted *T*-3 is often present and is sometimes associated with a low or flat *T*-2.

The relative incidence of myocardial damage or of position of the heart as a cause of low *T*-waves depends on the type of material being studied. The high percentage of cases with low *T*-wave, showing evidence of cardiovascular disease from ward and clinic sources might be interpreted as indicating that small *T*-waves are to be regarded as strong evidence of cardiac damage.* If, on the other hand, one's observations were limited to a group of presumably well individuals, the inference might be drawn that the chief cause of low *T*-waves is abnormal position of the heart.

The problem might, however, be considerably simplified from the standpoint of electrocardiographic interpretation if it were not for a group of cases in which there is no evidence either of myocardial damage or abnormal position of the heart. In our Group IV it would appear that a number of cases fall in such a category although the actual percentage is small. There are several possible explanations for such cases: (1). Myocardial changes may be present but

* The assumption that low *T*-waves found in cases showing cardiac disease are necessarily due to myocardial damage cannot be established. Thus, it is possible that in mitral stenosis the frequent finding of a low *T*-1 is more often dependent on altered position of the heart than on damage of the myocardium.

not recognized clinically;* (2) there may be enough rotation of the heart, without definite assumption of a vertical or horizontal position, to modify the *T*-waves;† (3) small *T*-waves may occur independently of myocardial abnormality or altered position of the heart.

Summary. 1. A vertical or transverse position of the heart has a marked influence upon the ventricular waves of the electrocardiogram. In vertically placed hearts *R*-1 is frequently low and often a low *T*-1 is associated. In transversely placed hearts *T*-3 is very frequently inverted and is sometimes associated with a low *T*-2; in many cases these findings are also associated with left axis deviation.

2. Although the association of low *T*-1 and *R*-1 is frequently encountered in vertical hearts it is also found in the presence of cardiovascular damage, especially in rheumatic heart disease.

3. The association of a low *T*-1 and high *R*-1 is usually encountered in cases showing some cardiovascular abnormality, especially hypertension. It has, however, been observed in a few cases in which no cardiovascular abnormality was demonstrable.

4. The incidence of definite cardiovascular abnormality found in cases referred from wards and out-patient clinics for electrocardiographic study which could be classified in one or another of the electrocardiographic types under consideration was as follows: Type A (Low *T*-1 and normal *T*-2) 83%; Type B (low *T*-1 and *T*-2) 87%; Type C (normal *T*-1, low or flat *T*-2 and inverted *T*-3) 63%. In cases derived from the same sources but with normal electrocardiograms, the incidence of definite cardiovascular abnormality found was 41%.

5. The percentages obtained for the incidence of myocardial damage or position of the heart as the cause of the low *T*-waves of the type classified under A and C depends mainly on the type of material being studied. In groups of presumably normal individuals, position is the more important; in groups suspected of heart disease, myocardial damage is the more important. In certain cases with heart disease, however, the *T*-wave changes may be due to altered position of the heart rather than myocardial damage *per se*. We have obtained no evidence to indicate that small *T*-waves in all leads may be dependent on position of the heart.

6. Roentgen ray study of the heart is essential in attempting to evaluate the significance of low or flat *T*-waves in either Lead I or Lead II of the electrocardiogram.

7. For guidance in the clinical interpretation of electrocardiograms we believe the following statements are justified:

A. An electrocardiogram with a low *R*-1 and low *T*-1 and a

* The not infrequent association of severe illness with small *T*-waves in all leads suggests that in such cases the myocardium may have suffered from the effects of the illness. In a number of such cases followed for months up to a year or more after recovery, the electrocardiogram has returned to normal. A normal electrocardiogram has been obtained in some cases soon after recovery.

† Certain electrocardiographic changes associated with the production of artificial pneumothorax support this view. (Unpublished observations, Edeiken and Lieberman.)

normal *T*-2 points either to abnormality of the heart or to vertical position. When the heart is vertically placed no significance can be ascribed to these findings as evidence of cardiac abnormality. When, however, the heart occupies its usual position, the low *R*-1 and *T*-1 suggest that it may be abnormal.

B. The association of a normal or high *R*-1 and a low *T*-1 offers strong but not certain evidence of cardiac abnormality.

C. The finding of small *T*-waves in all Leads is probably rarely if ever dependent on position of the heart. It furnishes strong presumptive evidence of abnormality of the heart.

D. The combination of a normal *T*-1, a low or flat *T*-2 and an inverted *T*-3 may be due either to abnormality of the heart or to a more transverse position than is usual. When the heart is transversely placed, such an electrocardiogram may not be regarded as evidence of myocardial abnormality; when, however, the heart occupies the usual position, such a tracing suggests myocardial abnormality.

E. It is possible that in a small minority of cases, these various types of electrocardiograms may occur in the absence both of altered position of the heart and abnormality of the myocardium.

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THE ELECTROCARDIOGRAM IN ACUTE EXPERIMENTAL DISTENTION OF THE RIGHT HEART.*†

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These experiments were carried out to determine whether significant electrical deviations accompany acutely developed distention on one side of the heart. A long time, often a number of years, is required for the development of a marked shift in the

* Aided by the Emil and Fanny Wedeles Fund of the Michael Reese Hospital for the Study of Diseases of the Heart and Circulation.

† This report is the completion of a study begun by one of us (W. C. B.).

electrical axis in the human heart, although very rapid shifts occur that are not easily accounted for except on the basis of a change in the heart's position.

Several types of experiments were performed. In the first group of experiments, 15 adult unanesthetized dogs, weighing between 7 and 26 kg., were used. In each, 5 cc. of metallic mercury were injected into a leg vein, and the hind leg was then elevated to facilitate the passage of the mercury to the heart. Metallic mercury was used because the obstructive effects of the metal following its widespread dissemination into the arterial side of the pulmonary circuit should lead to an acute right-sided distention. Its fluidity would avoid contact trauma. Electrocardiograms (standard leads) were obtained in the right and left lateral decubitus positions, before, shortly after and, provided the animal survived, 24 and 48 hours after the injection. In 10 animals the leads were taken in succession, in 5 they were recorded simultaneously (Leads I and II) by two electrocardiographs. The electrical axes were determined only on those curves satisfying with only slight error Einthoven's formula ($E^1 = E^2 + E^3$). The distribution of the metal and the heart size were determined by fluoroscopy and Roentgen ray examinations. Autopsies were done on all animals and the weight and mercury content of the hearts determined. Three other animals were used (which were sacrificed within 10 minutes after mercury injection) to determine the acuteness with which the changes occurred in the thoracic viscera.

In a second group of experiments, 4 dogs anesthetized with morphin and barbital were used. The chest was opened and artificial respiration instituted. The effect of mercury injections on the pressure curves of the two ventricles was determined by optical recording with Wiggers' manometers simultaneously with the taking of the electrocardiograms. In these animals the effect of almost complete occlusion of the pulmonary artery by clamp was determined on the electrocardiogram and intraventricular pressure curves.

Results. The results in the first group of animals are summarized in Table 1. It will be seen that the average survival period of the 15 animals was 35 hours following the injection of mercury, and ranged from 5 to 102 hours. Symptoms were scarcely noticeable for 15 or 30 minutes, sometimes an hour or more after the injection. Dyspnea was absent or, if present, was very slight. Fluoroscopy at this time, however, revealed a fairly widespread dissemination of the metal even into the smaller pulmonary radicles (Fig. 1). The first symptoms that usually appeared were gastro-intestinal, with retching and vomiting. Nearly all of the animals were observed to defecate within an hour after the injection. In a few animals there was marked muscular collapse and prostration. Six or more hours after the injection, dyspnea became marked, there was cough and grunting respiration, nasal discharge and later cyanosis of the mucous membranes. The animals ate and drank very little.

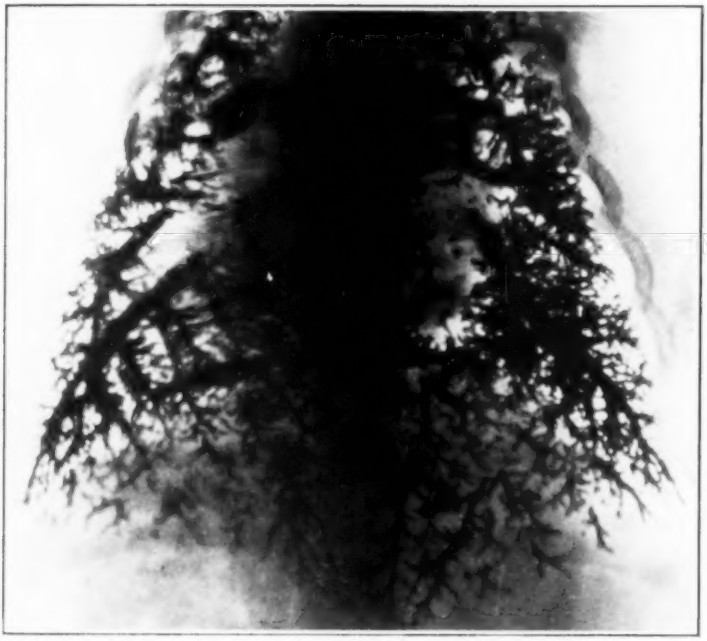

FIG. 1.—Roentgen ray of chest (24 hours after a 5 cc. metallic mercury injection), showing widespread distribution of mercury in pulmonary vessels. Note the mercury in the right auricle and ventricle.

FIG. 2.—Microscopic appearance of myocardium following mercury injection. Note the very marked hyperemia.

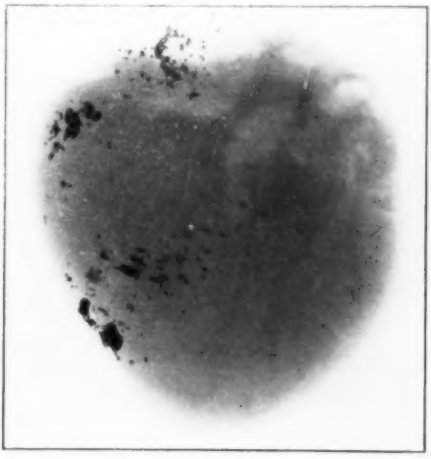

FIG. 3.—Roentgen ray of heart removed post-mortem, showing the distribution of mercury in the right auricle and ventricle.

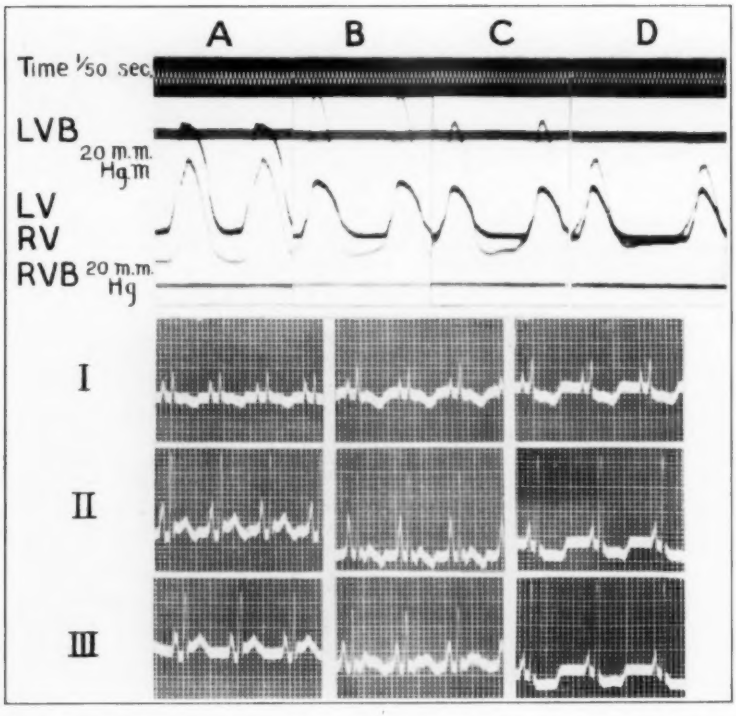

FIG. 4.—Simultaneous intraventricular pressure curves and electrocardiograms, showing effect of almost complete compression of the pulmonary artery. The intraventricular curves were recorded on a separate camera and are reduced to one-quarter their original size. The electrocardiograms are three-quarters natural size. Segment A is the control taken before compression, but some time after mercury injection. (This explains the relatively large systolic pressure in the right ventricle.) Segments B, C and D were taken 5, 10 and 30 minutes after compression of pulmonary artery. *LV* is the pressure curve of the left ventricle and *LVB* its base line. *RV* is the pressure curve of the right ventricle and *RVB* its base line. *I, II, III* are Leads I, II and III, respectively, of the electrocardiograms. No electrocardiograms were taken when Segment D was recorded. In Segments B, C and D, *RV* starts below *LV*, but crosses and goes above it during systole. The calibration of each pressure curve is given by the vertical line which represents the displacement caused by 20 mm. Hg. Note the appearance of a negative *S–T* in Segment C, which is probably due to the relative ischemia of the heart.

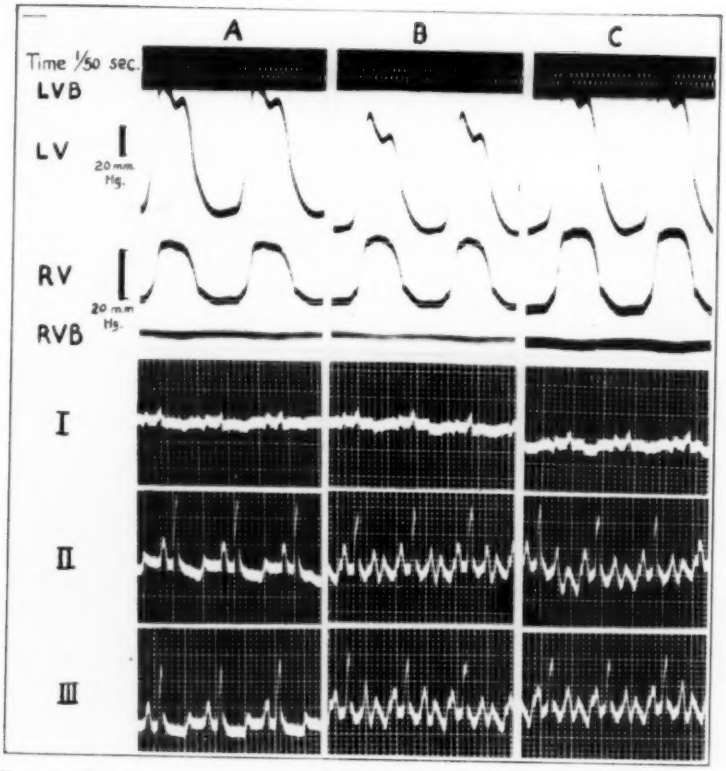

FIG. 5.—Simultaneous intraventricular pressure curves and electrocardiograms arranged as in Fig. 4, showing effect of mercury injection. Segment A is the control. Segments B and C were taken 1 and 5 minutes after mercury injection. Labeling and calibration as in Fig. 4.

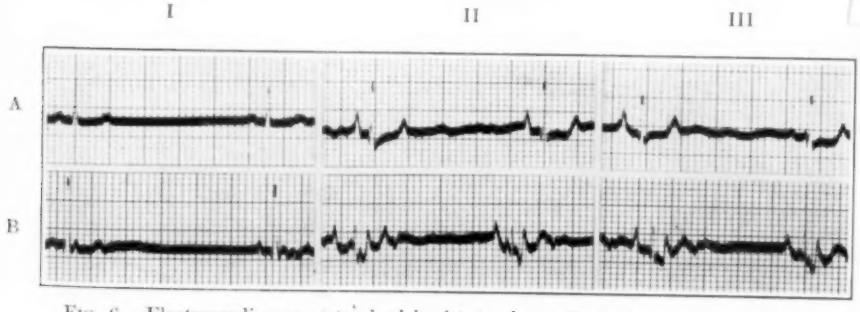

FIG. 6.—Electrocardiogram (standard leads) to show effect of mercury injections. Segment A control, B after mercury.

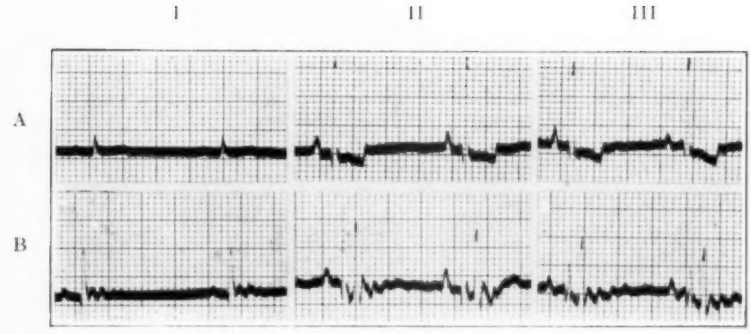

FIG. 7.—Electrocardiogram (standard leads) to show effect of mercury injections. Segment A control, B after mercury.

FIG. 8.—Electrocardiograms (standard leads) to show effect of mercury injections. Segment A control, B after mercury.

The essential changes at autopsy were, as expected, found in the thoracic viscera. There was marked dilatation of the right auricle and ventricle in all of the survival experiments. This was more prominent in those animals that survived a day or more. The left ventricle did not appear to be dilated. Small epicardial hemor-

TABLE 1.

Dog No.	Wt., kg.	Heart weight, gm.	Hg in right heart, gm.	Survival period, hrs.	Electrical axes. Animal on right side. Control, angle °.	5 to 10 min. after Hg, angle °.	24 hrs. after Hg, angle °.	48 hrs. after Hg, angle °.	Animal on left side. Control, angle °.	5 to 10 min. after Hg, angle °.	24 hrs. after Hg, angle °.	48 hrs. after Hg, angle °.
1	18.3	151.1	0.110	21	68	79	..	..	69	56		
2	15.0	20.0	0.063	28	60	79	..	..	79	70		
3	14.8	118.3	0.250	60								
4	10.1	86.1	0.084	8	61	85	..	..	70	81		
5	12.6	107.0	1.190	14								
6	21.2	138.1	4.180	27								
7	26.2	219.1	0.510	102	78	77	79	83	98	60	82	84
8	21.0	131.1	0.033	68	69	79	66	..	79	66	78	
9	9.7	101.1	0.710	5								
10	19.6	136.2	2.810	18	54	49	..	..	77	69		
11	9.9	84.7	0.022	29	*52	51	38	..	48	41	55	
12	9.3	123.2	0.303	17	*56	51	..	..	72	42		
13	15.7	148.2	0.207	62	*58	59	58	66	53	55	49	51
14	7.3	72.0	0.042	48	*71	84	66	..	44	58	66	
15	9.9	96.0	0.670	18	*60	71	..	..	57	53		
				Animal Sacrificed.								
16	8.7	75.3	3.327	10 min. after injection.								
17	8.9	69.1	0.390	8 min. after injection.								
18	27.8	202.0	0.221	8 min. after injection.								

* Leads I and II recorded simultaneously with two machines.

rhages occurred in the basal portions of the ventricles of several dogs in which the survival period was relatively long. No endocardial hemorrhages occurred. Microscopic sections disclosed intense hyperemia (Fig. 2). Although no epicardial or endocardial hemorrhages were noted in the hearts of the 3 animals used in the acute experiments, a microscopic section of portions of both right and left ventricles revealed marked capillary engorgement and diffuse intramuscular hemorrhage.

Formed thrombi containing mercury droplets filled the auricular appendages of more than $\frac{1}{2}$ of the animals (Fig. 3). In several there were small mural thrombi in the ventricles. A small amount

of mercury in the superficial coronary veins* was noted in 2 hearts. Approximately $\frac{1}{4}$ of the mercury injected, or about 15 gm. ($\frac{1}{6}$ or $\frac{1}{8}$ of the entire weight of the heart) was recovered from the right chambers after death, least being found in those animals surviving longest. A little more than $\frac{1}{3}$ of the injected mercury was recovered from the hearts of those animals immediately sacrificed. (The amount of mercury recovered from each heart, the weight of the heart and the survival period of the animal are given in Table 1.) There were a few mercury droplets of minute size, scarcely visible to the naked eye, in the left ventricles of 2 animals. The greater part of the mercury retained in the right auricle and ventricle was in the form of small droplets lodged in the recesses of the columnæ carneæ (Fig. 3). Larger accumulations seen in the apical portions of the heart may have been dislocated from the columnæ carneæ or from some pulmonary vessel.

The lungs were voluminous, wet and heavy, and usually did not collapse on opening the chest. They were the seat of infarctions. They were extensively mottled and colored purple, especially over the lower parts. There were extensive areas of consolidation throughout the lung fields. Several hundred cubic centimeters of a serosanguineous or fibrosanguineous fluid were present in the pleuræ of those animals that survived more than 24 hours; in 1 it was purulent. The lungs of the 3 animals immediately sacrificed appeared to be little less injured than those that survived many hours.

The changes noted in the other organs were essentially those of passive hyperemia and edema. The kidneys were not enlarged and the capsule stripped readily. There was no fluid in the pericardium and no inflammation about it.

Heart Size and Distention. Marked dilatation occurred regularly in the 5 animals that survived the injection of mercury for 24 hours. This was apparent on Roentgen ray examination and was found postmortem to involve the right heart. Dilatation was found in the other animals postmortem, even in the 3 sacrificed within 10 minutes of the injection of mercury. However, in the last animals the dilatation might have been agonal, especially in the animals where ether was used as the lethal agent. Roentgen rays of the dogs shortly after the injection of mercury failed to disclose any dilatation and, in the open-chested dogs, no dilatation was seen following mercury injection. It is, therefore, concluded that the dilatation of the right heart following mercury injection is a late phenomenon requiring a number of hours to develop.

In the open-chested animal experiments, tremendous right-sided dilatation at once followed the compression of the pulmonary artery. This procedure interfered so much with the output of the heart that the coronary flow was soon diminished and, as a conse-

* This may have entered by a reversal of flow in these veins, such as Batson and Bellet[2] appear to have shown, or *via* the Thebesian channels as suggested by the work of Bohning, Jochim and Katz.[3]

quence, the dilatation shortly involved the entire heart. The stage of right-sided dilatation was distinct, however, and lasted an appreciable interval of time. This unilateral dilatation was accompanied by a rise in the diastolic pressure in the right ventricle and a greater increase in the systolic pressure (Fig. 4, Segments A and B). At the same time the diastolic and systolic pressure of the left ventricle fell. Later the pressures in the left ventricle continued to fall, while those in the right ventricle decreased also, to even below normal (Fig. 4, Segments C and D).

In the open-chested animal experiments, mercury injections caused an immediate and persistently increasing rise in the diastolic and systolic pressure of the right heart (Fig. 5) and a temporary fall in these pressures in the left ventricle. Presumably the same change occurred in the survival experiments in the first hour. The development of dilatation which occurred later in the survival experiments is due no doubt to weakening of the heart muscle by the action of the mercury.

Electrocardiographic Changes. Inspection of Table 1 and the electrocardiograms of Figs. 5 to 8 show that neither in the survival experiments nor in the acute open-chested animal experiments was there recorded any significant right axis deviation, even when there was marked dilatation of the heart.

Shortly after the injection of the metal in the animals which survived, a slight shift of the electrical axis to the right usually occurred when the animal lay on the right side, and a slight shift of about equal magnitude usually to the left occurred when the animal lay on the left side (Tables 1 and 2). The axis deviations at the end of 24 hours in the animals which survived were not significantly different from those found within 10 minutes after mercury injection. Considering the errors involved in measuring the angles and the theoretical inaccuracy of the concept of the Einthoven triangle, the changes are not of especial significance.

TABLE 2.—SHIFT IN ELECTRICAL AXIS BETWEEN CONTROL CURVES AND VARIOUS TIMES AFTER INJECTIONS OF MERCURY.

Animal No.	Animal on right side.			Animal on left side.		
	Control and 5 to 10 min., angle °.	Control and 24 hrs., angle °.	Control and 48 hrs., angle °.	Control and 5 to 10 min., angle °.	Control and 24 hrs., angle °.	Control and 48 hrs., angle °.
1	+11	..	..	−13		
2	+19	..	..	− 9		
4	+24	..	..	+11		
7	− 1	+ 1	+5	−38	−16	−14
8	+10	− 3	..	−13	− 1	
10	− 5	..	..	− 8		
11	− 1	−14	..	− 7	+ 7	
12	− 5	..	..	−30		
13	− 1	0	+8	+ 2	− 4	− 2
14	+13	− 5	..	+14	+22	
15	+11	..	..	− 4		

\+ = shift in electrical axis to right.
− = shift in electrical axis to left.

The electrical axis was found to differ in the control curves, depending on whether the animal lay on its right and left side, respectively (Tables 1 and 3). This difference in electrical axis

TABLE 3.—SHIFT IN ELECTRICAL AXIS WHEN ANIMAL MOVED FROM RIGHT TO LEFT.

Animal No.	Control, angle °	After Hg injection: 5 to 10 min., angle °	24 hrs., angle °	48 hrs., angle °
1	+ 1	−23		
2	+19	− 9		
4	+ 9	− 4		
7	+20	−17	+ 3	+ 1
8	+10	−13	+12	
10	+25	+20		
11	− 4	−10	+14	
12	+16	− 9		
13	− 5	− 4	− 9	−15
14	−27	−26	0	
15	− 3	−18		

\+ = shift in electrical axis to right.
− = shift in electrical axis to left.

was slightly increased, as a rule, after the mercury was injected. This was no doubt due to the relatively heavy weight of the mercury ($\frac{1}{3}$ to $\frac{1}{6}$ the weight of the heart) within the heart. Some exceptions were noted and occasionally the difference was in the direction opposite to that anticipated. This confirms the observations of Meek and Wilson,[4] Nathanson,[5] and Katz and Ackerman,[6] who demonstrated that displacements of the heart around its antero-posterior axis either to the right or left do not always give the shift in electrical axis anticipated. Such anatomic rotations were prevented in the open-chest animal experiments by fixing the heart with the intraventricular manometers and a pericardial "cradle." The electrocardiographic curves in these experiments did not show any appreciable electrical axis shift, even with the extreme ballooning out of the right side of the heart which occurred following compression of the pulmonary artery (Fig. 4).

A rather characteristic aberration of the ventricular complexes was observed following the injection of mercury. During each systole of the heart, sharp notchings of short vibration period occurred. In some these were small in amplitude, resembling the distortions due to muscular tremor, except for the slower frequency (Fig. 7); in others they were larger and fewer in number, resembling diphasic extra *T* waves (Figs. 4, 5 and 6); and in still others they were so large as to resemble extra *Q–R–S* or *Q–R–S–T* complexes (Fig. 8).

Comment. There are no published data known to us in which the electrocardiographic effects of dilatation of the heart alone are clearly set forth. Herrmann and Wilson[7] have emphasized that shifts in the electrical axis seldom or never develop suddenly, and that the relative weight of the two ventricles may be one of many

factors which exert an influence on the electrical axis. This influence predominates only when the heart is greatly hypertrophied. The theory advanced by Fahr,[8] that shifts in the electrical axis may be produced by dilatation of one of the ventricles, has no experimental support. The results of Lundy and Woodruff,[9] that right and left axis deviation in the intact dog under ether anesthesia can be produced by distention of the respective ventricles, cannot be accepted as proof positive, as they themselves recognized. The electrical changes might have been produced by interference with the circulation of the heart itself or by possible effects of pressure on special structures within it. Some of these untoward features have been obviated in the experiments reported by us. However, in the animals which survived the injection, evidence of injury to both ventricles was found in the form of intense hyperemia and hemorrhage (Fig. 2).

The distortions of the ventricular complexes observed in these experiments are due to the short-circuiting effects of the mercury within the heart and lungs. They cannot be due to ventricular systoles, for they would have to occur while the ventricles are in the absolute refractory phase, obviously an impossibility. Furthermore, it can be shown that similar distortions can be produced by spraying the heart with mercury or by putting mercury into the pericardial sac (Jochim, Katz and Mayne[10]). It is unlikely that these short-circuitings may have altered the amplitude of the *Q–R–S* deflections unequally in the various leads, and so masked significant shifts of the electrical axis of the heart. In the experiments of Jochim, Katz and Mayne,[10] mentioned above, spraying the heart with mercury and placing mercury in the pericardium lead to no axis shift. Furthermore, it should be emphasized again that no axis shift occurred when the right-sided dilatation was produced by compression of the pulmonary artery.

Summary. 1. The production of diffuse pulmonary emboli of metallic mercury following its introduction directly into the right heart or systemic venous circulation causes acute distention of the right heart. In the more chronic experiments a marked degree of right-heart dilatation is regularly produced.

2. Instrumental compression of the pulmonary artery produces a marked ballooning out of the right side of the heart, followed soon after by a similar ballooning of the left side.

3. Acute distention or dilatation of the right heart in the above experiments is accompanied by no significant deviation of the electrical axis of the heart.

4. The peculiar aberration of the ventricular complex (*Q–R–S–T*) produced by mercury injection are illustrated, and evidence is presented to show that they arise because of short-circuits set up by the intracardiac and extracardiac metal.

The negative *S–T* segment following occlusion of the pulmonary artery (*cf.* Fig. 4) resembles the changes observed by Feil, Katz, Moore and Scott (Am. Heart J., 1931, **6**, 522) when the vena cava is occluded.

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NOTE ON ELECTROCARDIOGRAPHIC CHANGES ACCOMPANYING ACUTELY INCREASED PRESSURE FOLLOWING PULMONARY ARTERY LIGATURE.*

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Changes in the electrical axis of the ventricles (altered weight relations, shifts in position) have long been known to produce characteristic changes in the electrocardiogram. The electrocardiographic changes that follow sudden increase of intraventricular

* Acceptance for publication of the preceding article in this number by Buchbinder and Katz recalled germane studies which had been made at Harvard in the summer of 1916, but, due to the disturbance in scientific work brought about by the World War, had never been completed. Inasmuch as there is apparently little published on the electrocardiographic effects of acute increase of intraventricular pressure, it would seem as if a short note might add to the evidence available on this problem. It is a pleasure to acknowledge, even at this late date, my debt to Dr. Alexander Forbes for his help, access to his string galvanometer and for the animals, many of which were used at the same time for his studies on the nerve impulse.

Legends for Figs. 1, 2, 3 and 4.

Fig. 1.—Exp. IV. Six records of Lead I only. Note change from an inverted to a prominent upright P wave, and the varying changes in the ventriculogram: diminution of R (No. 4), development of a slow S (No. 6), return of R on release of clamp (No. 9), finally complete A–V block with slow R and inverted T (No. 14). The T wave and the iso-electric period also show frequent changes. In this and subsequent records the string was standardized so that 1 M V = 2 cm. deflection (here reduced) and the film was run at the rate of 1 cm. per 0.01 second. Occasionally one complex in each strip has been retouched. The time marker has been omitted to save space.

Fig. 2.—Exp. VII. Note extreme development of S_1, with obliteration of T_1, disappearing on release of clamp (No. 28); development of S_2 and S_3 less marked; customary increase of P in all leads; in No. 27 marked slowing with extreme deflections; tendency for iso-electric period to disappear. In this and Fig. 4, to save time in shifting leads, records of Leads I, II and III were followed by the next set taken in reverse order (*i. e.*, Leads III, II, and I).

Fig. 3.—Exp. V. Four records of Lead II only. Note the increasing size of P in successive leads, also the change from a positive to a negative T (Nos. 2 and 11). In the final strip (dying heart) (No. 20), the rate is slow (ca. 45), all deflections are exaggerated and there is apparently an A–V rhythm.

Fig. 4.—Exp. VIII. Note numerous changes in T wave, also tendency for upstroke of S_1 (and downstroke of R_3) to go beyond previous iso-electric level. In the last 6 records (Nos. 62–74), it appears as if a 2 to 1 A–V rhythm had been established.

Fig. 1

Exp IV. No 1
L1 1.20 pm
Exp IV. No 4. 1.55 pm
Exp IV No 5
L1 1.57 pm
Exp IV No 6
2 pm
Exp 4 No 9
L1
clamp release
Exp IV No 10
2.15 pm
clamp tight
Exp IV. No 11
L1 2.50 pm
Comp block

Fig. 2

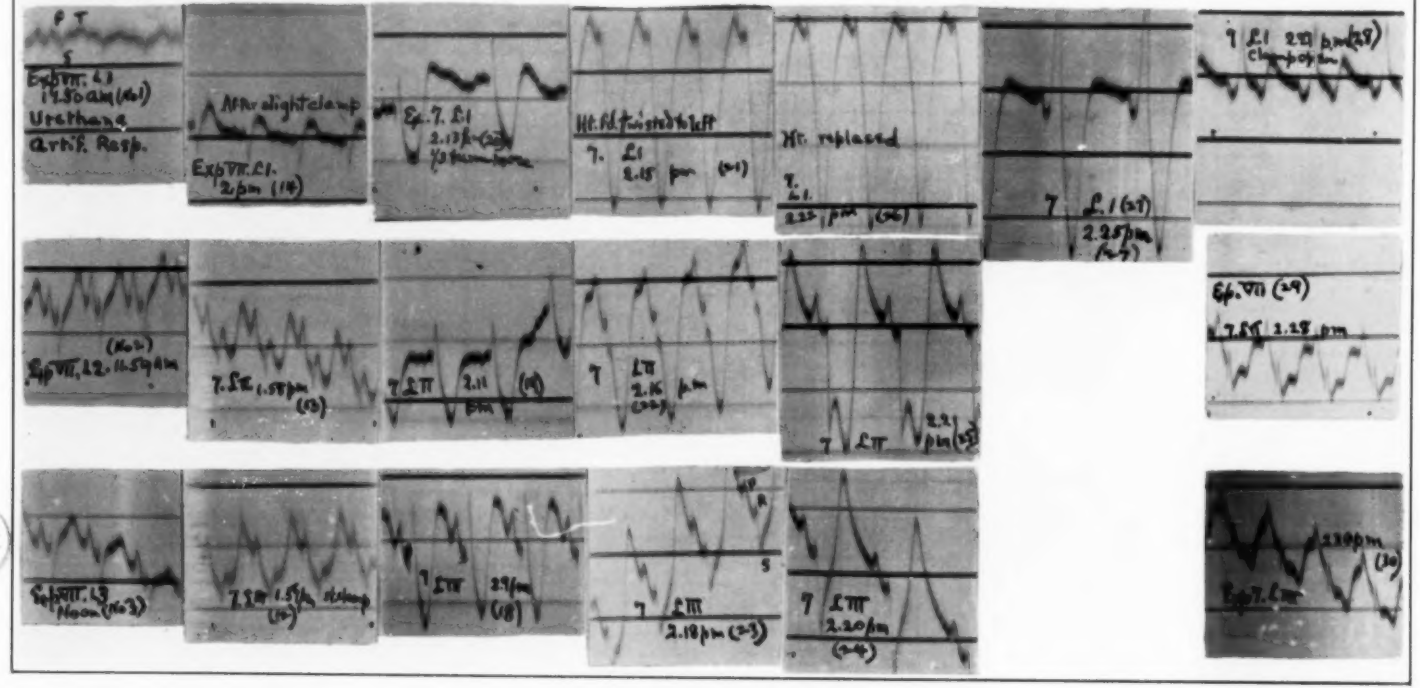
Exp VII. L1
11.30 am (No 1)
Urethane
artif. Resp.
After slight clamp
Exp VII. L1.
2 pm (14)
Ht. replaced
Exp VII. L2. 11.54 am
(No 2)
Exp VII (29)
Exp VIII. L3
11.00 am (No 3)
Exp 7. L1
Ht. replaced
7 L1
2.25 pm
7 L II
7 L III
2.18 pm (23)
7 L III
2.20 pm
(24)
2.30 pm
(30)

FIG. 3

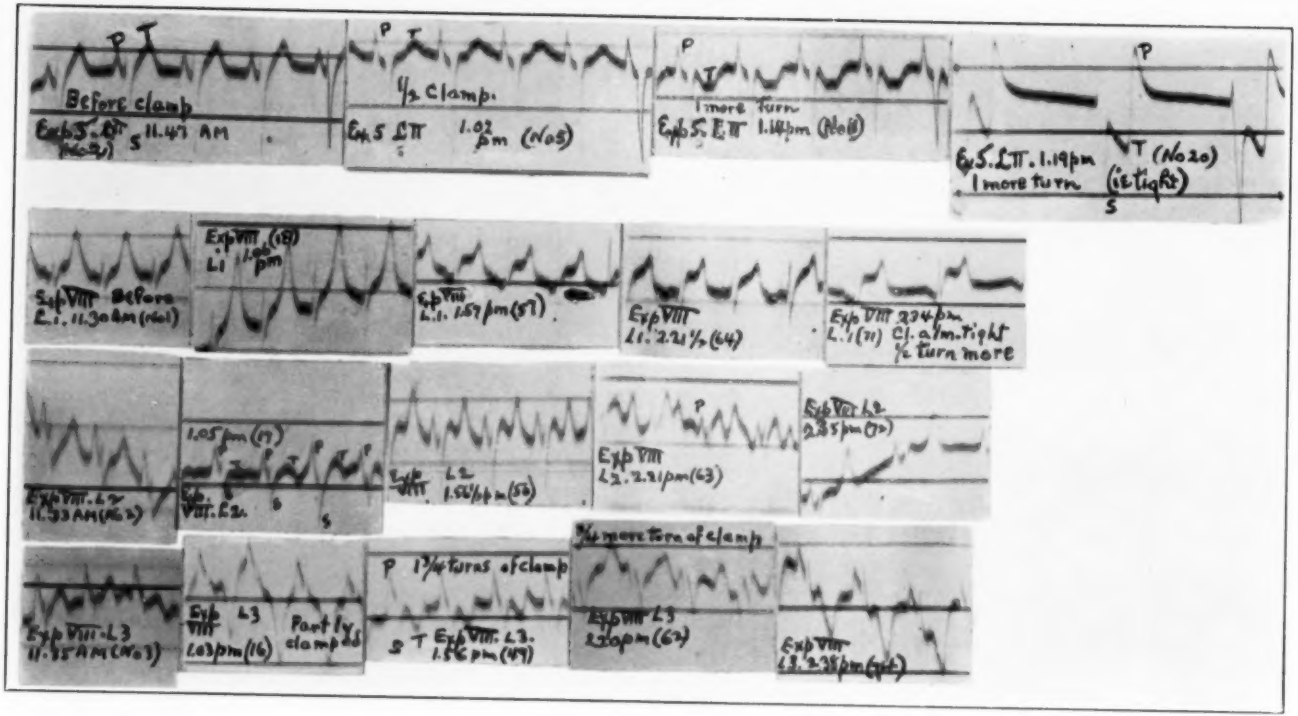
Before clamp
Exp 5. Lt 11.47 AM
½ Clamp.
Exp 5 Lt 1.02 pm (No5)
1 more turn
Exp 5. Lt 1.14pm (No6)
Exp 5. Lt. 1.19pm
1 more turn
T (No20)
(it tight)
S

FIG. 4

Exp VIII Before
L1. 11.30 am (No1)
Exp VIII (52)
L1 1.08 pm
Exp VIII
L1. 1.57 pm (57)
Exp VIII
L1. 2.21½ (64)
Exp VIII 2.34 pm
L1 (71) Cl. a/m. Tight
½ turn more
Exp VIII. L2
11.33 AM (No2)
1.05 pm (17)
Exp VIII. L2.
Exp VIII L2
1.50 pm (58)
Exp VIII
L2. 2.21 pm (63)
Exp VIII. L2
2.25 pm (70)
Exp VIII. L3
11.35 AM (No3)
Exp VIII L3
1.03 pm (16)
Partly clamped
P 1¾ turns of clamp
S T Exp VIII. L3.
1.56 pm (49)
¾ more turn of clamp
Exp VIII L3
2.30 pm (67)
Exp VIII
L3. 2.38 pm (74)

pressure (before compensatory hypertrophy can occur) do not seem to have had equal attention (see preceding article).

In an attempt to study the effect on the electrocardiogram of such rapidly increased intraventricular pressure, records were taken before and after varying degrees of pressure were exerted on the pulmonary artery. Ten anesthetized cats, some decerebrated under anesthesia, had funnel-boot electrodes inserted beneath the skin of both fore legs (on flexors) and left hind leg (on gastrocnemius or vastus), for employment of the three customary leads, the cat lying on the left side. After control records were taken, the thorax was opened under artificial respiration, a Gaskell clamp loosely applied to the pulmonary artery a few centimeters above the valves, and the heart maintained as nearly as possible in its normal position. After another control record, increasing amounts of constriction were exerted by means of the clamp, and records taken as frequently as possible after each quarter turn of the screw. Sometimes records were taken until the artery was clamped tight; at others when dilatation of the right ventricle occurred visibly, the process was reversed, again with records. Sometimes the experiment was concluded by the occurrence of ventricular fibrillation, or by A–V block with increasing slowing of the rate; at others it was possible to repeat the sequence after all pressure had been removed.

It was recognized that the numerous manipulations, occasional asphyxia, hemorrhage, and slight and varying changes in position of the heart in the opened thorax in themselves might produce changes in form of the ventriculogram, though the importance of such items was not appreciated to the extent that it is today. These disturbing factors, plus the varying changes due to differences in speed of increasing pressure on the artery, could account for our inconstant results, which were not possible to solve in the few experiments that circumstances permitted. However, while control experiments, such as shifting body position, gave minor changes in form, they never produced the marked changes shown in these records, changes which largely or wholly disappeared on releasing the clamp. (See Buchbinder and Katz's more detailed observations on this point in the preceding article.) It is safe to conclude that the effect of increasing pressure within the right ventricle, as practised here, was regularly to increase the size of the P wave in all leads and frequently to produce extreme ventricular deflections like those seen in congenital heart disease. Sometimes signs similar to those of preponderance of the right ventricle (in the old sense) appeared, and disappeared when the clamp was loosed. When the clamp was about $\frac{3}{4}$ closed, the right ventricle usually became much congested and dilated with a slow beat, and the electrocardiogram sometimes showed a deep broad S_1, a high broad R_3 and in Lead II a deep Q, medium R and no S. The possibility of such changes being due to bundle branch block must of course be borne in mind. The reason why these changes only appeared occasionally was not apparent; and it should

be noted that they are not in accord with Buchbinder and Katz's observations. The *T* wave, when not engulfed in the preceding *S*, sometimes became enlarged, sometimes inverted or diphasic, sometimes coming off near the point of *R* or *S* respectively, or at a new level from an overshoot of *R* (or *S*) or finishing at a new iso-electric period. Small extra waves, as if continuations of the *T* disturbance, were sometimes noted (see No. 63) similar to those discussed by Buchbinder and Katz. It is suggested that changes in the ventricular complex, perhaps resembling those of right or left ventricular preponderance, especially if transient, *may* be due to changes in intraventricular pressure and not always to changes in muscle mass or position of the heart.

It was observed with the naked eye that after prolonged dilatation the auricle beat regularly after the ventricle had stopped, then slowed and stopped also. On two occasions distinctly visible contractions of the superior vena cava were observed, a few centimeters above the junction with the auricle. These were thrown in between the auricular beats (1:8, 1:10, etc.) but stopped 2 and 3 min. before the auricle stopped. It was not possible to record them electrocardiographically.

While obviously no conclusions can be drawn from so few experiments with varying results, it is suggested that more extensive studies, better controlled, of increasing pressure in right or left ventricle should throw light on the nature and significance of abnormal ventricular complexes.

ARTERIOSCLEROSIS OF THE LUMBAR SEGMENTAL ARTERIES PRODUCING ISCHEMIA OF THE SPINAL CORD AND CONSEQUENT CLAUDICATION OF THE THIGHS.

A Clinical Syndrome With Experimental Confirmation.*

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Dejerine's syndrome[1] in the syphilitic of "intermittent claudication of the spinal cord" characterized by recurring weakness in the lower limbs on exertion, but which was unaccompanied by cramps or by obliteration of arterial pulsations in foot and ankle,

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was recently observed in 4 non-syphilitic patients who showed roentgenographic evidence of marked arteriosclerosis of the lower abdominal aorta. An ischemia of the spinal cord due to arteriosclerotic involvement of the segmental branches from the aorta was postulated to explain this syndrome, and ligation of these arteries confirmed this hypothesis by producing an identical syndrome in the experimental animal.

Historical. Discussions of the effects of arteriosclerosis of the vessels of the spinal cord are conspicuously absent in modern textbooks or monographs of neurology, although the literature of the past century contained many reports of symptoms referable to this condition. More recently there has occurred a revival of interest in the subject and a number of articles have appeared on focal lesions of the cord due to arterial disease[2,3,4,5] and on the resemblance of the early lesions of multiple sclerosis to those of experimental vascular occlusion.[6]

Intermittent Claudication of Local Vascular Origin. The early descriptions of intermittent claudication were written by neurologists. Charcot[7] in 1858 first described the syndrome in the horse and in man. He found occlusion of the peripheral arteries with ischemia of the muscles and nerves of the legs. In 1862 Raynaud[8] introduced the elements of vasomotor spasm due to dysfunction of the sympathetic nervous system into the problem, and Erb[9] in 1898 was one of those who added the third type of peripheral vascular disease known as thrombo-angiitis obliterans. Intermittent claudication was explained by some observers on the basis of inadequate blood supply to active muscles, by others to disturbances of innervation. In a similar way the origin of the pain of angina pectoris was debated. To add to the confusion, Dejerine (1894) described a rare form of "intermittent claudication of the spinal cord." Only recently has Thomas Lewis[10] demonstrated that intermittent claudication (and probably angina pectoris as well) is to be attributed to pain which is "determined by some chemical or physico-chemical agency within the mass of muscle."

Paraplegias. In addition, certain paraplegias have been attributed to ischemia of the extremities or of the spinal cord. Thus, in 1857, Gull[11] wrote of a sudden paraplegia with paralysis of the sphincters, and anesthesia of the lower extremities in which arterial pulsations were absent. There was a rapid but incomplete recovery, and a tremendous development of subcutaneous collateral arterial circulation. "Examination of the case . . . . made it probable that the paraplegia had arisen from some sudden deficiency of arterial supply to the lower extremities, as in the experiment by Sir Astley Cooper of ligature of the abdominal aorta in a dog." On the other hand, Gowers[12] suggested disease of the small arteries in the spinal cord as a cause of senile paraplegia characterized by progressive weakness of the legs and no changes in the reflexes. Bramwell[13] stated in 1886 that "paraplegia sometimes results from

the sudden stoppage of the blood supply to the lower end of the cord, an accident which occurs in the course of some abdominal aneurysms in consequence of detachment of the clot or obstruction of the abdominal aorta. In some cases of aortic regurgitation, weakness in the lower extremities—never, so far as I know, amounting to true paralysis—is seen. The motor weakness probably results from anemia of the lumbar region of the cord." Bristowe[14] invoked both peripheral vascular ischemia and ischemia of the spinal cord to explain 3 cases of paraplegia following sudden obstruction of the abdominal aorta by aneurysm (1881).

Blood Supply of the Spinal Cord. The most valuable description of the vascular supply of the spinal cord is given by Moxon.[15] "The blood-supply to the spinal cord is carried out by slender vessels which come from the vertebral arteries within the cranium. There are 3 of these arteries—1 on the front and 2 on the back of the cord; they are very slender, and yet have to run along its whole length." Since pressure in these spinal arteries falls rapidly, reinforcing arteries (the cervical, intercostal, lumbar and sacral segmental vessels from the aorta) are sent up along each segmental set of nerve roots. "But when you approach the tip of the cord the supply from below becomes exceedingly precarious, and even apt to fail entirely, because upon the long strands of the cauda equina the small arteries are too narrow and too long to reinforce the cord with any certainty. But at the same time the supply from above has to be furnished with greater difficulty than in the upper regions of the cord, because the original anterior spinal artery is very far away, and the reinforcing arteries even in the lumbar region have to run considerably longer courses than they had in the cervical region . . . . Hence we see that the tip of the spinal cord corresponding to the lower limbs and sphincters is much more weakly organized as to its circulation than are the upper parts of the cord." Moxon supplemented his theory with injected specimens—the lower part of the cord was consistently poorly injected (even though the cannula was at the femoral artery), and "in no case were the reinforcing vessels on the nerves of the cauda equina injected."

He explained the selective weakness of the posterior members of animals following small doses of prussic acid and drugs which lower blood pressure to the peculiarities of the vascularity of the spinal cord.

Intermittent Paraplegias. Moxon[15] presented a highly interesting discussion of the intermittent paraplegia and incontinence of caisson disease. Quoting Captain Eads (chief engineer of the Mississippi bridge at St. Louis) he says "'When the depth of 60 feet had been attained, some few of the workmen were affected by a muscular paralysis of the lower limbs. This was rarely accompanied with pains, and generally passed off in the course of a day or two. As the penetration of the pier progressed the paralysis became more

FIG. 1.—Bismuth arterial injection 1 day after division of abdominal aorta, showing good vascularity of thighs and legs. Incontinence and paralyzed lower extremities were present.

"It is in the highest degree probable that we here have to deal with a malarial infection; the intermittency of the paroxysms, their termination in a sweat, and the efficacy of quinine, all argue strongly in favor of this intermittent paraplegia being nothing else than a masked intermittent. To be sure, this cannot, as yet, be considered as rigidly proven.

"It may probably be even more positively asserted that the seat and starting-point of this disturbance is to be found in the spinal cord. The entire character and grouping of the symptoms, the limitation of the paralysis to purely spinal nerves, the entire immunity of the brain, the great resemblance to other general paralyses of notoriously spinal origin, speak with such positiveness in favor of this belief that no reasonable doubt on the subject can be raised.

"But it is, unquestionably, a matter of the greatest difficulty to determine what actually takes place within the spinal cord in this malarial paraplegia—whether any, and, if so, what anatomical changes take place therein during the attack. Hartwig assumes that it is a question of transitory hyperemias and serous transudations in the substance of the spinal cord; a supposition which appears to me untenable, from the mere fact that the disturbance is always confined to the motor portions of the cord, leaving the sensory portions entirely free. It is probably safer to say that the essential conditions of malarial spinal paraplegia are at present unknown to us, and that we can only hope for light on this subject from the future."

Two years later, Laveran discovered the parasite of malarial fever (1880); today all textbooks of pathology picture the capillaries of the brain and viscera plugged with pigment and parasites. We may now explain these cases of intermittent malarial paraplegia on the basis of ischemia of the spinal cord as the result of such plugged vessels, with remission accompanying the vasodilatation of the sweat.

Dejerine's Intermittent Claudication of the Spinal Cord. According to Dejerine[1,17] this rare condition is due to a progressive occlusion of the lumina of the arteries to the lower cord, attributed to an arteritis, presumably syphilitic. The disease begins with a weakness, often unilateral, on exertion of the legs. The weakness soon becomes bilateral and develops more promptly on walking. A few minutes of rest permits recovery, progressively less complete. When the resting patient is examined, nothing is found; during a period of fatigue, a certain degree of spasticity may be evident. Soon the tendon reflexes are somewhat hyperactive in repose, more so after walking. At this time the sign of Babinski appears on exertion, to disappear with rest. Deep and superficial sensibility is intact. Urinary symptoms appear, with loss of libido or with hyperexcitability and premature ejaculation; the sphincter ani may or may not escape. Finally a permanent spastic paraplegia supervenes.

Dejerine sharply separated this syndrome from Charcot's intermittent claudication. The distinguishing features of the disease of the spinal cord are the integrity of the arterial pulsations of the lower extremities, the absence of pain and of vasomotor disturbances, and above all the presence of neurologic symptoms: altered reflexes, impairment of sphincter control and genital disturbances. He also differentiated from his syndrome those of pseudoparalytic myasthenia gravis (Erb-Goldflam) and of arteriosclerosis of the vessels accompanying the peripheral nerves; in the spinal cord syndrome, atrophy and changes of electrical reactions are absent, and tendon reflexes are not lost.

Intermittent Claudication of the Thighs Due to Ischemia of the Spinal Cord. We have recently seen 4 patients with the syndrome described by Dejerine produced by an arteriosclerosis rather than by syphilis of the spinal cord. In all cases, roentgenograms showed advanced calcification of the terminal abdominal aorta, and in each case there was neither history nor clinical evidence of syphilis. In the absence of autopsy material, we were able to verify experimentally the hypothesis that intermittent claudication of the thighs was due to ischemia of the spinal cord the result of occluded arteriosclerotic lumbar segmental arteries or their branches to the spinal cord. The vascular supply to the muscles involved in this claudication was unimpaired.

Experimental Confirmation of Claudication of the Thighs from Ischemia of the Spinal Cord. Weakness of the hind limbs after complete occlusion of the aorta was repeatedly recorded in the protocols of adult animals in Professor Halsted's article[18] in 1909 on partial, progressive and complete occlusion of the aorta and other large arteries in the dog by means of the metal band. As an example, in his Dog 2 with partial occlusion followed in a month by complete occlusion of the abdominal aorta, it was noted "1 hr. after operation the dog was able to climb a flight of stairs. The hind legs were in a spastic condition, flexed on the abdomen, at the knees and hips, and were very much weaker than the fore legs." Forty-eight hours after occlusion "hind legs are dragged in walking but are not completely paralyzed. Movements still spastic." On the 6th postoperative day "bladder and rectum function normally. Scratches himself with left hind leg without apparent weakness." The weakness of the hind limbs suggested an investigation of the spinal cord which was entrusted to Dr. P. K. Gilman "who discovered, in several instances, about 3 months after total or almost total aortic occlusion, a deposit of extradural fat about the cord below the site of the aortic band. In 3 cases the production of fat was so great that it filled, seemingly under considerable tension, the vertebral canal."

Professor Halsted's interest in the collateral circulation after occlusion of large arteries led to a report by Reichert[19] in 1924 in which, among other sites of ligation, the abdominal aorta was ligated in ten instances. "In these studies young dogs were used since adult animals not infrequently show evidence of spinal cord

changes." The study of any effect upon the spinal cord was not undertaken at that time; however, it was the impression in the laboratory (on obtaining apparently good arterial injections of the tissue distal to the aortic occlusion in some adult animals) that the weakness and spasticity of the hind limbs could not be due to impaired blood supply to their musculature but was probably caused by ischemia of the spinal cord.

When the first patient (Case 2), with claudication due to weakness of the thighs, tabetic type of gait, and calcification in the lower abdominal aorta, was studied, these earlier observations in the dog came to mind and the problem was taken to the laboratory. The details of the experimental work will be published separately[20] and only a summary of the results will be given here.

The problem resolved itself into determining the effect on the hind limbs (1) of ligation of the abdominal aorta alone, (2) of aortic ligation in conjunction with ligation of one or more lumbar segmental arteries, and (3) of ligation bilaterally or unilaterally of one or more lumbar segmental arteries. The effects of the ligations were carefully observed by exercising the animals and having them climb stairs. When sacrificed, the whole arterial system was injected through the heart with Poth's[21] modification of Hill's[22] bismuth oxychlorid mass, opaque to the passage of Roentgen rays. Stereoscopic roentgenograms were examined to determine circulatory alterations following ligation. The spinal cord and its coverings were excised, roentgenograms taken to show its arterial injection, and section of the cord studied microscopically and by the clearing method of Spalteholz.[23]

Ligation of the Abdominal Aorta. In our previous experiments[19] it was shown that some degree of collateral circulation was normally present when the aorta was injected immediately after its ligation and division, the bismuth appearing in the trifurcation and its branches well down into the legs. Injections made 10 to 12 days after ligation showed complete filling of the vessels distal to the ligation.

In the present study the abdominal aorta was ligated in 3 adult dogs. One old dog who was paralyzed and incontinent was sacrificed and injected 24 hr. after division of the aorta. The roentgenograms (Fig. 1) showed good arterial injection in the thighs and legs but not equal to that in Fig. 2 where the aorta was intact. The day after ligation the remaining 2 dogs walked poorly, dragging the hind legs. Only a few steps were climbed before the hind quarters gave way. The following day they were unable to climb, weakness of the hips was quite noticeable, and a scissor-like gait appeared. By the 7th day after ligation they were up and about with definite but slight weakness of the hind limbs and slight swaying of the hips. After 2 weeks the hind limbs seemed spastically extended, with stiffness noticeable in the upper thighs.

Bilateral Ligations of Lumbar Arteries. In 5 adult dogs one or

more pairs of lumbar segmental arteries were occluded as they branched from the aorta. A very old dog, after ligation of 1 right and 1 left lumbar artery, was totally paralyzed in her hind limbs and was incontinent. When injected 24 hr. after ligation the arterial filling of the thighs and legs (Fig. 2) was excellent indicating that the palsy could not be due to impaired vascularity of the musculature. After the same type of ligation in an old dog weakness of the hind limbs developed which was similar to that noticed after ligation of the abdominal aorta. This weakness was slight after the 5th day and could not be detected at the end of a month. In a young adult animal weakness of both hind limbs was evident for 3 days after ligation of a lumbar artery on each side. A week later 2 distal lumbar arteries on each side were ligated but no weakness developed. Roentgenograms of the injected animal showed that considerable collateral circulation had developed after the first ligation, which was adequate in supplying the region involved in the second ligation. In another young adult animal, when 4 lumbar arteries on one side and only 1 artery on the other side were ligated, the weakness of the thighs and legs seemed equal but the subsequent stiffness was possibly more marked on the side of the 4 ligated arteries. In the 5th animal when 3 lumbar arteries were ligated on each side the weakness gradually improved over a period of 2 weeks, with spasticity appearing 2 days after ligation. Climbing a short flight of stairs could not be accomplished until the 8th day after ligation.

Comment. The ligation of one or more paired lumbar arteries produced effects almost identical and as severe as after ligation of the abdominal aorta. In fact, in a very old dog ligation of a single pair of lumbar arteries caused paralysis and incontinence; yet the roentgenograms of the injected animal (made 1 day after ligation) showed no interference with the circulation to the lumbar region or the hind limbs, although the ligated arteries were not as fully filled with bismuth as the adjacent ones. Development of sufficient collateral circulation through the adjacent lumbar arteries in the other cases seemed to explain the improvement in symptoms that occurred within a week after ligation.

These experiments produced symptoms similar to those observed after ligation of the abdominal aorta and the arterial injections proved that it was not the impaired circulation to the musculature in either case but the ischemia of the spinal cord that produced the weakness of the hind limbs.

Ligation of the Abdominal Aorta and One or More Lumbar Arteries. Ligation of the abdominal aorta has never produced gangrene, nor does gangrene occur after ligations of 3 pairs of lumbar arteries. In 2 of 3 experiments in which in addition to aortic ligation one or more pairs of lumbar arteries were also occluded, complete paralysis and incontinence resulted with massive gangrene developing distally from the midabdominal region. The young adult animal that

survived had marked weakness of the hind limbs and was incontinent for a day. Three days after ligation his hind limbs were stiff and he would take only a few steps. Four days later he walked readily but with stiff hind limbs, and awkwardly went up and down stairs. Ten days after ligation he walked and jumped about readily and showed only a slight weakness of the hind limbs on climbing stairs.

Unilateral Ligation of Two or More Lumbar Segmental Arteries. In 4 animals 2 lumbar arteries and in 1 animal 3 lumbar arteries on 1 side only were ligated. All had weakness and some stiffness of the corresponding hind limb lasting from 3 to 8 days.

Comment. This ipsolateral weakness and spasticity after unilateral ligation of 2 or 3 lumbar segmental arteries added further proof to the preceding results that ischemia of the spinal cord produced the weakness of the hind limb, since the roentgenograms of the injected animals showed no impairment of the arterial supply of the involved musculature at the time of greatest weakness (2 or 3 days after ligation).

Summary of Experimental Results. In adults dogs the signs of weakness of the hind limbs, especially in the hips and thighs, accompanied at times by temporary incontinence, and associated with a delayed spasticity, invariably followed either ligation of the lower abdominal aorta or ligation bilaterally of one or more lumbar segmental arteries. Ligation of one or more lumbar arteries on one side only invariably produced weakness of the ipsolateral hind limb. In these experiments exercise resulted in weakness only, never any apparent pain. Bismuth arterial injections made through the heart filled the entire arterial system as shown in the stereoscopic roentgenograms and revealed that the weakness was not caused by inadequate blood supply to the involved muscles but could only be due to ischemia of the spinal cord. With the development of adequate collateral circulation through adjacent lumbar arteries the signs rapidly improved.

The chief complaint of our 4 patients was weakness on exertion of the upper thighs, especially of the anterior group of muscles. That type of pain characteristic of the ordinary intermittent claudication was conspicuously absent. The neurologic examinations revealed only hyperactive deep reflexes. Blood and spinal fluid examinations were negative for evidence of syphilis and of pernicious anemia. Signs and symptoms of generalized arteriosclerosis were obtained and all exhibited calcification of the terminal abdominal aorta in the roentgenogram.

Case Reports. Case 1.—(E. L. B.) Mr. F. O. S., aged 69, when first examined March 30, 1927, presented a history of 3 years' duration of a gradual increase in the feeling of numbness of the bottoms of both feet (although sensation was normal) and marked weakness of both quadriceps muscles. These symptoms were preceded by cerebral arterial trouble with diplopia and hypertension. After slight exercise considerable weakness of the quadriceps and other thigh muscles developed which left him unable

to control his legs and feet. Urinary symptoms (hesitancy and difficulty in feeling the passage of urine) were present for several years. There was no pain.

Examination revealed generalized arteriosclerosis with pulsations in the pedal arteries much decreased but still palpable. The thighs and legs seemed spastic, and the weakness of the thighs with inability correctly to place the feet presented a gait resembling that of a tabetic. The reflexes were hyperactive. There were no signs and the examinations were negative for pernicious anemia and for syphilis. The prostate was twice normal size. Roentgenograms showed definite calcification of the lower portion of the aorta just above the bifurcation.

Comment. In the presence of generalized arteriosclerosis one explanation for the claudication in the thighs would be sclerotic changes in the vessels to these muscles, but the absence of pain, the patent pedal arteries, the feeling of numbness in the feet although the sensation was normal, the difficulty in recognizing the passage of urine, the steppage gait, and the calcification of the abdominal aorta strongly favored an ischemic condition of the spinal cord as the correct explanation.

Case 2.—(D. A. R. and F. L. R.) Mr. A. B., aged 53, a salesman, entered the neurologic wards of Lane Hospital December 1, 1932, complaining of burning in the legs and feet and inability to control his lower extremities when walking, for 2 years. Weakness and cramps developed in his thighs and legs on walking up an incline or up steps. When climbing stairs it was necessary to use the hand rail, as his hips and knees would give out and he would collapse. After walking 2 or 3 blocks his thigh and calf muscles would tighten and become painful so that he walked stiffly. The pains in the thighs were mainly anterior. Bowel trouble, described as a sense of fullness in the rectum and soiling of the linen, was another complaint. The diagnosis of tabes by the examining officer was made from his gait and could not be confirmed in the ward. Complete examinations ruled out pernicious anemia and syphilis. There were no neurologic signs except hyperactive reflexes. Pulsations of the dorsalis pedis artery were absent on the right and barely perceptible on the left. Roentgenograms taken of his pelvis because of pain and weakness in the hips were negative except for calcification in the terminal abdominal aorta and right iliac artery (Fig. 3).

In an attempt to relieve his claudication a bilateral alcoholic sympathetic block at the level of L_1, L_2 and L_3 was made which warmed both feet and toes and relieved the burning sensation. Six weeks later pulsations were readily felt in the left and just perceptible in the right dorsalis pedis artery, but he had no definite improvement in the claudication.

Comment. This patient with claudication of the hips and thighs, stiffness of the limbs, and calcification in the abdominal aorta reminded us of the dogs reported by Dr. Halsted with weak hind limbs after occlusion of the abdominal aorta and led to the experimental study of signs obtained from vascular impairment of the spinal cord summarized in the preceding section. His syndrome was a combination of the ordinary type of intermittent claudication with pain in the muscles, with claudication due to weakness but without pain; the former is attributed to ischemia of the muscles,

the latter to ischemia of the spinal cord. In this patient, both types occurred together or alone at various times.

CASE 3.—(F. L. R.) Dr. S., aged 57, noticed early in January, 1932, that walking 10 blocks easily fatigued him and produced dizzy spells with nausea and vomiting. On January 18 he developed a coronary occlusion with a systolic pressure of 80. Four days later the systolic pressure was 100 to 106. During the 5th week he could not get comfortable in bed, feeling the substernal pain and pain in the back, particularly between the shoulders, or pain in the gluteal region.

Within a ½ hr. after sitting up on the edge of the bed for the first time in 10 weeks he suddenly coughed up blood tinged sputum and later noted a tingling sensation in the fingers of the right hand and in the toes and sole of the left foot. This sensation continued for 3 weeks and gradually disappeared, to reappear and remain for over 1½ years. At the same time the skin of the left upper chest was extremely painful to the slightest touch. Frequently pain of a burning character would extend down both arms as far as the wrists.

Frequent blood-pressure readings taken as soon as the patient became comfortable after paroxysmal attacks of weakness almost invariably showed the systolic reading at 100 or less, and when he was feeling fairly well this pressure varied from 110 to 125.

When seen on April 8, 1933, he had been complaining for several months of weakness of both thighs, difficulty in walking on the level with shuffling of his feet and inability to walk up hill or up stairs. Pulsations were readily obtained in the feet and ankles, and the reflexes were hyperactive. The tingling sensation in the right hand and left foot persisted.

The history of weakness in both thighs was similar to the complaint of the previous patient so that there was no surprise when roentgenograms revealed calcification in the abdominal aorta and some of its pelvic branches, and also in the left coronary. On a month's régime to maintain and increase his blood pressure, walking improved and the gait became spastic, suggesting even to him that of a tabetic, although all examinations for syphilis were negative.

Comment. A subnormal blood pressure with periods of markedly low systolic readings prevailed throughout his convalescence. The evidence of arteriosclerosis in the abdominal aorta, yet with excellent arterial pulsations obtainable in the extremities, would favor the diagnosis of ischemia of the spinal cord as the cause of the claudication of the thighs and the "tabetic" gait.

CASE 4.—(E. L. B.) Dr. W., dentist, aged 45, was referred by Dr. L. Falk February 13, 1933. In July, 1932, the patient gradually experienced tiredness in the anterior portion of both thighs on walking, especially up hill. There had been no cramps in the calves nor any neurologic symptoms.

The examination showed absent pulse in both dorsalis pedis arteries and in the left posterior tibial vessel. The pulsation in the right posterior tibial artery was barely palpable. His blood pressure was 155 systolic, 100 diastolic. The reflexes were all present, equal, and hyperactive. Physical and serologic examinations were negative for syphilis. Roentgenograms of the lumbar spine, thighs, and legs showed definite calcification of the aorta from the third lumbar vertebra down to the bifurcation, with no evidence of sclerosis in the peripheral vessels.

Comment. Claudication limited to the thighs without arteriosclerotic symptoms elsewhere and with calcification of the arterial

tree limited to the lower abdominal aorta is difficult to explain except as an ischemia of the spinal cord.

Conclusions. The ordinary intermittent claudication in the arteriosclerotic is characterized by pain which is attributed to physiologic processes developing in the working muscles easily fatigued due to impaired blood supply. It is associated with a lack of arterial pulsation in the feet and ankles, color alterations in the skin of the extremities on change of posture, and roentgenographic evidence of calcification in the arteries of the legs.

Intermittent claudication because of weakness in the thighs and hips was the chief complaint of 4 non-syphilitic arteriosclerotic patients who exhibited a spastic gait resembling that of a tabetic, who had no positive neurologic signs, and whose roentgenograms revealed calcification in the lower abdominal aorta.

The claudication of the thighs in these 4 patients was attributed to ischemia of the spinal cord produced by alterations in spinal branches of the arteriosclerotic lumbar segmental arteries arising from the abdominal aorta.

This hypothesis was strengthened by roentgenographic evidence of calcification in the terminal portion of the abdominal aorta and by experimentally produced claudication in the thighs of adult dogs after occlusion of the lumbar segmental arteries without interference with the blood supply to the thighs or remainder of the lower extremities, as shown roentgenographically by complete arterial injections of the animals.

Unilateral claudication developing after ipsolateral occlusion of one or more lumbar arteries in the dog afforded further proof that ischemia of the spinal cord was the cause of the claudication.

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THE TREATMENT OF ARTERIOLAR HYPERTENSION WITH CRYSTALLINE OVARIAN HORMONE (THEELIN).

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A causative relation between the endocrine system and arteriolar (essential) hypertension has often been suggested and in some cases proven. In one group of cases, namely, hypertension associated with tumors of the suprarenal gland, the evidence of an etiologic relationship is adequate.[1] The ovaries have often been mentioned as concerned in the development of arteriolar hypertension, but there is very little evidence. In an analysis of 1230 menstrual and sex histories taken with this possible endocrine relation in mind, Alvarez and Zimmerman[2] found that hypertensive women showed a much higher incidence of sexual abnormalities such as uterine fibroids, a masculine distribution of body hair and sexual anesthesia as compared with women having normal blood pressures. These investigators believed their evidence supported the theory that arteriolar hypertension is a "bodily peculiarity inherited equally by girls and boys, but ordinarily repressed in women before the menopause by the ovarian or other related secretions." Such a theory explains why arteriolar hypertension increases in frequency at and beyond the time of the menopause. Also, the absence of the female sex hormones in men may be the reason why arteriolar hypertension begins earlier in men.

Which one, if any, of the sex hormones, is related to the development of arteriolar hypertension is also a surmise. Since it is known that, at the time of the menopause, the ovaries atrophy and their secretions probably cease, it is possible that the ovarian hormones are the ones concerned in the development of the disease. In the past, various investigators have reported that extracts of the ovary lower blood pressure, but it is now recognized that these preparations were inert or contained non-specific vasodilators such as cholin.[3] Recently, Doisy[4] isolated the first female sex hormone in crystalline form, the ovarian follicular hormone called Theelin. Several studies have already been made concerning the effect of this hormone on the

blood pressure. Laquer[5] using a preparation called Menformon, which is probably the same as Theelin, found no effect on the blood pressure of animals. Melchionna,[6] using Theelol intravenously, also found no effect on the blood pressure of anesthetized animals. However, Crainicianu[7] and his coworkers have reported strikingly different results. These investigators, using Menformon and Hogival brands of the hormone, found that a drop in blood pressure followed the intravenous injections of 100 rat units in animals, especially in females. In addition, Crainicianu studied the effect of 100 rat units injected intravenously into 100 human subjects with apparent success except in castrated women. Unfortunately, these apparently important results of Crainicianu are presented in such a way as to make anyone familiar with the variability of both normal and high blood pressures, highly skeptical of the method by which Crainicianu obtained his results. He did not mention that he in any way controlled the study of his subjects' blood pressure before giving the injections of hormone. The cautions needed for any study of blood pressure have frequently been emphasized.[8]

Present Investigation. In the present investigation, the effect of the ovarian follicular hormone upon the blood pressure, catamenia, and symptoms of patients with arteriolar hypertension has been studied. The ovarian follicular hormone used is marketed under the names of Theelin and Theelol.* Both Theelin and Theelol are each a distinct crystalline chemical compound, the Theelin being active only on hypodermic injection, whereas, Theelol is active when administered by mouth. Theelin was supplied in 1 cc. ampules containing 50 rat units. The Theelol was used in two different strengths, a tablet triturate containing 100 rat units, and in capsules each containing 50 rat units.

The small number of patients used for this study seems well compensated for by their variety and by the length of their control observation prior to this study. Of the 10 patients studied, whose ages varied from 36 to 60, 2 were males and 8 were females. Of the 8 females, 3 had not reached the menopause while 5 had long passed the menopause. The renal function was normal in all the patients. Electrocardiograms in 9 of the patients showed that the only abnormality (in 5 patients) was moderate left axis deviation. Teleoroentgenograms taken in all the patients showed moderate cardiac enlargement in 5 patients. In 6 of the 10 patients, the ocular fundi showed moderate to marked narrowing of the arterioles, while in Patients 7 and 9 there were little or no change.

All of the patients had been seen by the author over a period of at least 1 year before this study, and during that time had each made an average of 11 visits at average intervals of 1 month. On each of these visits during the year preceding this study, the blood-pressure measurements were made in the same way as during the present study—as follows: On arriving at the clinic or office, the patient sat resting until his turn for examination. Then after entering the examining room, and lying down on a table, his blood pressure was taken at once by the author. Then he was urged to relax and allowed to rest alone in the examining room. At intervals of 10 min. the blood pressure reading was taken over a period of 20 min. In 9 of the patients the systolic pressure was above 160 mm., and the diastolic above

* Dr. E. A. Sharp, of the Parke, Davis & Co., supplied generous amounts of the hormone.

95 mm. while in Patient 9 the systolic reading fluctuated between 140 and 160 mm. and the diastolic 80 to 94 mm.

In addition to this average control period of 1 year, during which little or no medication had been given, a special 3 to 4 weeks' control period was instituted before the start of Theelin therapy (Table 1). At start of this

TABLE 1.—AGE, SEX, DOSAGE AND DURATION OF TREATMENT WITH THEELIN AND THEELOL OF PATIENTS WITH ARTERIOLAR HYPERTENSION.

Patient No.	Age.	Sex.	Period of water injections (weeks).	Amp. 1 (50 R. U.) daily of Theelin (weeks).	Amp. 2 (100 R. U.) daily of Theelin (weeks).	Additional daily dosage (weeks).
1	58	M.	4	5	2	
2	43	F.	3	3	5	100 R. U. Theelin by injection + 200 R. U. Theelol by mouth (4 weeks)
3	57	F.	4	6		
4	60	F.	4	4		
5	47	F.	3		5	
6	49	M.	4	3	5	
7	36	F.	4	3	4	50 R. U. Theelin by injection + 300 R. U. Theelol by mouth (2 weeks)
8	59	F.	4	4	2	
9	48	F.	4	3	3	
10	43	F.	4	4	3	

special control period, the patients were taught how to give themselves subcutaneous injections. They were then given 7 ampules each containing 1 cc. of distilled water, and were instructed to inject into themselves daily the contents of 1 ampule. The ampules were of the same size and appearance as the ampules of Theelin later used. The patients returned each week for study of their blood pressure and to receive a supply of ampules of distilled water. The patients, of course, were unaware that they were using distilled water. Thus, this control period permitted proper evaluation of the effect of the frequent visits[8] and supposed treatment[8] upon their symptoms and blood pressure.

Then, without the patient's knowledge, the distilled water ampules were changed to ampules of Theelin, and the routine of weekly visits continued. The Theelin and Theelol treatment was continued for from 1 to 3 months in the different patients. Since stopping the treatment the patients have continued under regular monthly observation for at least 7 months. The dosage administered (Table 1) was varied at different times and in the different patients. In most of the patients, following the control period of distilled water, a daily subcutaneous injection of 50 rat units was taken over periods ranging from 3 to 6 weeks. Following this, the dose was raised to 50 rat units injected twice daily, and continued for 2 to 5 weeks more. Finally, 2 patients (Cases 2 and 7) received massive doses as follows: Patient 2, continued on for 4 weeks during her 3d month of Theelin treatment, with a dosage of 100 rat units Theelin daily by injection and 200 units daily of Theelol by mouth. Patient 7, after an 8-weeks rest period without treatment, took 50 rat units Theelin daily by injection plus 300 rat units of Theelol daily by mouth, for a period of 2 weeks. The largest total dosage was taken by Patient 2, who took 6335 rat units in a period of 3 months.

Results. In no way was any influence on the blood pressure noted. Chart I illustrates the manner in which the blood pressure was unaffected by treatment for as long as 3 months and with high dosage. In fact, during the 6 weeks' control period with distilled water, the blood pressure appeared to be lower, and then appeared to rise on starting Theelin treatment. However, this paradox

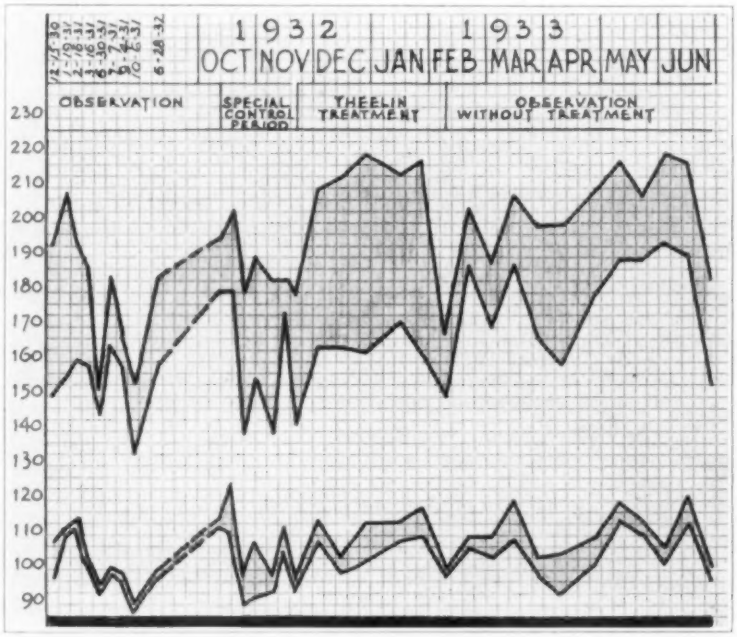

CHART I.—Blood-pressure readings of Patient 2 before, during and after Theelin treatment. The shaded area bounded by the 2 upper curves represents systolic variations, not only from visit to visit, but also after resting at each visit (the latter variations indicated by the vertical distance between the 2 curves). The shaded area bounded by the 2 lower curves represent the same for the diastolic blood pressure.

is due to the fact that during the control period the patient was seen at frequent (weekly) intervals, compared to once in 2 weeks when Theelin was started. The effect of frequent visits *per se* on the blood pressure has been demonstrated before by the author.[8] Most of these patients were symptomless, but as is expected,[8] some of them felt even better while taking the distilled water. In only 1 patient (Case 7) was any effect noted upon the menstrual cycle. In this patient, her second menstrual period after stopping treatment was prolonged from the usual 5 to 6 days to 10 days. This had never occurred before in this patient's catamenial history. However, at this time, she also had a severe attack of common cold. In this same patient, after an 8 weeks' period without treatment the

hormone was again given in large doses for 2 weeks. During the second week of this dosage, she had severe epistaxis twice and a gastro-intestinal upset consisting of epigastric discomfort, nausea, gaseous eructations and pyrosis. Her next catamenia was normal. The catamenia of the other patient receiving large doses was not affected nor were any symptoms produced. All of the female patients were questioned as to their sexual sensations and none admitted any change in sex desire during or after treatment.[9] Patient 4 developed a coronary occlusion during her second week of treatment with Theelin. There seems no reason to believe that the Theelin produced the coronary occlusion.

Summary. The effect of the crystalline ovarian follicular hormone (Theelin and Theelol) upon the blood pressure of patients with arteriolar hypertension has been studied. The daily use of this hormone over periods as long as 3 months and in daily doses as high as 350 rat units was without any discernible effect on the blood pressure of these patients.

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ERRORS OF SURGICAL DIAGNOSIS.

A Study of the Records of the First Surgical Division of The Roosevelt Hospital Covering a Period of 3 Years.

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As in most institutions of its kind, a regular weekly conference of each surgical division is held at this hospital. The list of operations performed during the week is read, together with a record of instances of lost asepsis, of institutional complications, and, most important of all, of errors of diagnosis. Mistakes of observation or of judgment are noted, commented upon and discussed with a view to the avoidance of similar errors in the future.

From the records of these conferences covering a period of 3 years the diagnostic errors of the First Surgical Division have been tabulated. The histories, physical findings, laboratory data, operative results and pathologic reports of the cases concerned have been reviewed and analyzed. In making this study three questions have been kept primarily in mind: What errors do we most commonly make? Why do we make them? and How may they best be avoided?

Method. These errors are determined as follows: Before each operation the anesthetist inquires of the operating surgeon: "What is the pre-operative diagnosis?" The surgeon's reply, his final and considered estimate of the situation confronting him, is entered on the anesthetist's chart and thus becomes a matter of record. At the conclusion of the operation the postoperative diagnosis is also asked for and entered. This latter diagnosis is also subject to confirmation by the subsequent pathologic report. A discrepancy between these recorded diagnoses represents a diagnostic error. If, for example, the diagnosis before operation has been chronic appendicitis and the condition is found to be acute, a diagnostic error is recorded. According to the rules such convenient subterfuges as "exploratory celiotomy" are not encouraged. Each patient is operated upon for some specific disorder which the operator must name. If the condition is not found as predicted, the surgeon must revise his estimate of the situation and seek the sources of his error.

Results. *Acute Appendicitis.* In reviewing the errors of these 3 years we find, as might perhaps be predicted, that acute appendicitis heads the list. Aside from the possible complications which may confuse the diagnosis of this condition, two important factors enter into this preponderance of error. The first is that numerically the operations for this condition exceed all others. The second, that it is a diagnosis, which, from the nature of the illness, must be made rapidly and when made, acted upon promptly. During the 3 years under consideration the diagnosis of acute appendictis has been made 389 times on our division, incorrectly in 28 instances; constituting an error of 7%. That this error is no larger speaks well indeed for the accuracy of succeeding house-surgeons, upon whose shoulders the determination of this diagnosis most directly falls.

Five times, in the 28 errors, acute salpingitis or salpingo-oöphoritis was mistaken for acute appendicitis. The signs and even the history of these two conditions may be very similar, even to the vomiting and early epigastric pain. The lady of Ethiopian antecedents and unconventional social habits may arouse our suspicion, or there may be a vaginal discharge, a tender fornix or an unusually low abdominal tenderness to put us on our guard. Sometimes these signs fail, however, and the differential becomes difficult. One sees, of course, instances of peri-appendicitis of pelvic origin, and on one occasion at least I recall a much inflamed ovary and tube which presented immediately upon opening the peritoneum in a McBurney incision,

while the appendix lay, quite harmless, low down in the pelvis. The hazards of acute appendicitis being what they are, it seems that we must continue to give the patient the benefit of the doubt in the questionable case even though this policy is productive of a certain margin of error.

The next most common source of error in diagnosing acute appendicitis lies in the appendix itself: 5 of our 28 errors occurred in cases where the appendix was not acutely inflamed, as predicted, but was pronounced "chronic appendicitis" by the pathologist. Such an error seems a little difficult to understand, and one would not be likely to expect that it would be made as often as confusing acute salpingitis with appendicitis. Yet it occurred just as frequently in this group. Perhaps a little light on this occurrence may be shed by referring to a case recently operated upon. In this patient, a child, the classical picture of an acute attack of appendicitis was present. Elevation of temperature, high white cell count and relative polynucleosis were all present as were local and rebound tenderness and rigidity. Yet the pain was not persistent, but came in cramplike spasms so suggestive of ureteral colic as to lead to a Roentgen ray examination before operation was undertaken. Yet this type of pain gave the clue to what was subsequently found at operation—a long appendix, containing fecoliths, markedly kinked near the base by a short mesentery. There was engorgement, but no acute inflammation, the case being one of true appendiceal colic and potentially, although not actually, acute appendicitis. The pathologist reported chronic appendicitis.

Our records bearing on this error indicate that 3 of the 5 cases recorded as wrongly diagnosed fell in this group of obstructed appendices, typified by the example cited. Such appendices may or may not go on to acute inflammation at the time or subsequently. They are probably safer out of the abdomen. The error of diagnosing them as acutely inflamed may perhaps be diminished by considering the duration of the attack and the character of the pain. There are many cases of true acute inflammation encountered in which a history of colicky pain early in the attack may be elicited.

The other 2 of the 5 errors in this group were in patients who had suffered previous attacks of appendicitis and in whom the severity of the current one was overestimated.

In the group of 28 errors there were 4 instances in which normal appendices were removed where the diagnosis was subsequently determined as enteritis. Three of these were in children. In looking back over these records one sees in each case symptoms, signs and laboratory findings sufficiently indicative of appendicitis to lead one fully to expect to find it. Perhaps we have become so imbued with the idea of the vital seriousness of appendicitis in childhood, that we are a little prone to forget that an acute gastro-enteritis may at times simulate it very closely, even to the blood count.

This attitude may be further strengthened by the experience of every surgeon, who can recall instances in which the classical evidence of acute appendicitis were wanting in greater or less measure—yet where fulminating appendiceal pathology was discovered at operation.

Usually, in gastro-enteritis, the rather early onset of diarrhea is a helpful point in our differentiation—yet even this fails us where the apparently inescapable and often lethal laxative has been administered. Further confusion arises from the fact that we occasionally see an appendicitis, especially in children, following and presumably having its inception in an enteritis.

Closely allied to the enteritis group in our record of errors are those cases, simulating appendicitis, in which, at operation, a typhlitis is found. This error occurred 3 times in the 3 years under consideration. Each time the cecum was found much reddened, with thickened serosa and injected vessels, while the appendix, obviously not the source of the difficulty, was but little if at all involved. One might perhaps have been warned in these cases by the fact that the blood counts were not elevated to the degree one might have expected from the severity of the symptoms and signs. Yet, unfortunately, such is often the case in true appendicitis. Although all of these patients survived (except 1 in whom the appearance of the cecum strongly suggested tuberculosis, and who was pregnant as well) they were not benefited by the removal of an appendix in a disease which would no doubt have subsided spontaneously.

The same may be said of the two children who were found at operation to be suffering from serous peritonitis instead of the appendicitis which they were supposed to have. In these cases the abdomens were quite full of straw-colored clear fluid and, except for a rather striking enlargement of mesenteric lymph nodes, no lesions were found. Cultures and sections of removed glands and of appendices revealed no clue as to the nature or cause of the difficulty, and we are still in the dark. Whether this is primarily an intestinal infection, a mild form of pneumococcus peritonitis, or a manifestation of the more or less apochryphal intestinal influenza we are unable to say.

Pneumonia was mistaken for appendicitis but once. Here the Roentgen ray has undoubtedly helped us in keeping the errors low by its ability, in suspected cases, to demonstrate pulmonary lesions before their physical signs become apparent.

Pelvic disease, other than salpingitis, has tripped us more than once, and until our gynecologic diagnostic ability has advanced beyond our present limitations and approaches that of the specialists in that field, will no doubt do so again. The record runs: hematometra, 1; papillary cyst—adenoma of ovary with twisted pedicle—1; ruptured chocolate cyst of the ovary, 1. Certainly, we are con-

vinced by our experience that no female patient should be operated upon for acute appendicitis who has not been accorded a vaginal, or, in the rare instances where this is injudicious, a rectal pelvic examination.

Acute cholecystitis, in low lying gall bladders, was twice mistaken for appendicitis. Ordinarily, the differentiation does not involve great difficulty, it would appear; but there are high placed appendices and gall bladders which descend almost to the pelvic brim to confuse us at times. Their variations between these extremes of position leaves room occasionally for doubt, but the hot gall bladder usually, wherever placed, presents a firm and exquisitely tender area close to the examining fingers, while the high appendix, retrocolic as a rule, withdraws its tenderness behind a shield of resistant muscles rather out toward the flank.

Two other errors in this group are mentioned merely as curiosities. In 1 case, a carcinoma of the transverse colon with acute obstruction and, in the other, an abscess in a right ectopic kidney were mistaken for acute appendicitis.

Chronic Appendicitis. The diagnosis of chronic inflammation of the appendix is one which is reached after considerably more deliberation than that of acute appendicitis. Not altogether undeservedly has this diagnosis diminished in popularity of recent years. The chronic appendix has no doubt covered a multitude of surgical sins in its time. Yet, recognizing this fact, there is still a pathologically and clinically demonstrable group of cases in which a diseased condition of the appendix is responsible for a definite set of symptoms. These are the cases suffering from repeated attacks of acute appendicitis, from more or less continued right lower quadrant pain, from vague digestive disturbances (of the appendix reflex type of which Brewer used to speak), from chronic constipation with pain which does not subside when the constipation is overcome. All of these show, in common, tenderness in the region of McBurney's celebrated point.

During these 3 years chronic appendicitis was diagnosed 213 times. The diagnosis was wrong 5 times—an error of 2.3%.

Three of these errors fall in the field of pelvic diagnosis. In 1 case a retention cyst of the right ovary was found. In 2, chronic salpingo-oöphoritis of the right adnexa was the lesion.

In a measure, the remarks made concerning the confusion of the diagnosis of acute appendicitis with pelvic trouble apply here. The patients in whom these errors were made were given pelvic examinations and reported normal. The observation was at fault. The interesting work, which is recently being done, of visualizing the pelvic organs for Roentgen ray by means of a lipiodol injection, may point the way to a greater degree of accuracy in our pelvic diagnosis in the future.

In 1 case, chronic cholecystitis was discovered at operation, in addition to the expected chronic appendicitis.

It would seem that these findings rather emphasize the importance of carefully investigating, as a matter of diagnostic routine in doubtful cases, the biliary system as well as the stomach and kidneys and ureters and pelvic organs before submitting the patient to an operation for chronic appendicitis. Such a procedure is now the practice on our division.

Two further errors must be recorded under this diagnostic group. In 1 case an appendiceal abscess was discovered, retrocecal and well localized, in a patient who entered on the third day of the last of a series of similar attacks with a temperature of 99°, but no mass was felt. The other, showing no lesion at operation, had the appendix removed prophylactically, and the pathologist failed to come to our rescue. I believe we are making the diagnosis of chronic appendicitis less frequently as our diagnostic methods improve.

Hernia. Next, in point of numbers, to our errors in the diagnosis of appendicitis, acute and chronic, come the mistakes in the diagnosis of hernia. Superficially, at least, it would seem that even a medical student should be able to diagnose hernia with reasonable accuracy, yet this apparently simple condition has with us a diagnostic error of 5%. In 292 cases in 3 years we were wrong 15 times. Yet, there is some consolation in the fact, perhaps, that the errors have shown a yearly decrease.

Two cases operated upon for inguinal hernia had enlarged rings but no hernial sac. One inguinal hernia with hydrocele proved to have the hydrocele but no hernia. Three supposed inguinal hernias, 2 apparently incarcerated, proved to be hydroceles of the cord. Two others proved to be femoral hernias instead of inguinal. One strangulated hernia diagnosed as femoral proved to be inguinal instead. Femoral hernia was also mistakenly diagnosed in 1 case each of femoral adenitis, inguinal adenitis, femoral varicosity, and psoas abscess. One supposedly strangulated umbilical hernia proved not to be strangulated, while one incarcerated inguinal hernia was mistaken for a varicocele.

This, one might say with reason, is hardly a record to be proud of. The mistakes involving adenitis, varicocele, hydrocele and a psoas abscess stand out like a sore thumb. An error of observation was undoubtedly responsible in each case. These mistakes emphasize the importance of considering seriously and eliminating the various pathologic conditions which may simulate hernia, and particularly the necessity of scrutinizing with greatest care those ostensible hernias which do not reduce. As to the elimination of negative findings at operation, we are now in the habit of making the patient demonstrate his hernia before we undertake repair. If he cannot cough it down or walk it down in the ward, he is likely to be requested to report again some day when the hernia is in view. This Missourian attitude will in the long run, I believe, save some unnecessary operations. We do not feel that an enlarged external inguinal

ring, or pain in the groin, is a satisfactory criterion of the necessity of repair.

Cholecystitis. Next in the order of frequency occur the errors in diagnosis of conditions of the biliary tract. Operation was done for acute cholecystitis but 9 times in the 3 years. In 1 the diagnosis was wrong. In this instance a high, acutely inflamed appendix closely simulated the clinical picture of a fulminating, possibly gangrenous cholecystitis.

For chronic cholecystitis 191 operations were done in the 3 years with 13 errors—an error of 6.05%.

In 2 of these cases no lesions were found to explain the symptoms and clinical findings. In one a gastro-enteroptosis of rather marked degree was discovered. One case had an acute suppurative cholecystitis, which, running an unusually quiet course, was thought to be a chronic inflammation. Two had duodenal ulcer, while the symptoms for which the operation was done were found to be due in the remaining cases to one each of the following conditions: chronic pancreatitis, chronic appendicitis, carcinoma of gall bladder, pelvic peritonitis, tuberculous retroperitoneal lymph nodes impinging upon the common duct. In 2 additional cases firm bands of adhesions across the duodenum were found, without demonstrable gall bladder lesion.

In the diagnosis of gall bladder disease it is perhaps more apparent than in any other abdominal field that one cannot depend wholly upon any single diagnostic method. While the history is often typical and characteristic, it alone may be misleading. Much as the Roentgen ray has done to help in the establishment of a correct diagnosis, especially since the introduction of the intravenous administration of tetraiodophenolphthalein, it is still only possible, often, to report that the suspected gall bladder does not fill and visualize properly. Such was the case in a number of the instances cited above, where an extrabiliary lesion rather than a cholecystitis was responsible for the failure to visualize. It is possible to approach accuracy in this diagnosis only where all findings and factors, clinical, anamnetic and radiologic, can be coördinated, and interpreted in their proper interrelationship to form a complete picture.

Here again, as in chronic appendicitis, an isolated study of the supposedly diseased organ will lead to diagnostic errors. The importance of including a full gastro-intestinal Roentgen ray study in the investigation of cases of suspected gall bladder disease is emphasized by the mistakes recorded. It will be recalled that 4 of the 13 errors represented the discovery of gastric or duodenal lesion instead of disease of the gall bladder. To be sure, this method was employed in the cases cited, as it is routinely on our service, in spite of which the errors occurred. The point is that there would certainly have been many more such errors (since the conditions can simulate each other so closely) were this examination not done.

Diagnosis of calculus in the common duct was made 13 times—erroneously in 3 instances. The error here was high, 23%.

One of these cases proved at operation to be acute yellow atrophy. Her history had strongly suggested common duct obstruction, with "indigestion" of 2 months' duration and right upper quadrant pain for 2 weeks, with vomiting and jaundice. On operation the liver showed characteristic changes. The other two had had previous cholecystectomies for cholecystitis and cholelithiasis and complained of recurring attacks of right upper abdominal pain associated with jaundice. Both were found to have dense adhesions partly or completely obstructing the common duct, and were relieved by operation. No stone was found.

In view of the difficulty of differentiating this latter condition from common duct stone, it might have been wiser to have limited our diagnosis to obstruction of the common duct. Neither of these cases showed the tell-tale Charcot fever which we are so likely to associate with the sudden occlusion of the duct by a ball-valve stone. The Roentgen ray, as yet, cannot help us in making this differentiation.

Duodenal Ulcer. Duodenal ulcer was the pre-operative diagnosis 64 times in this 3-year period. In 8 the diagnosis was not verified at operation, representing an error of 12.5%. In 1 case, the stomach and duodenum being found normal, the patient's complaint was ascribed to neurasthenia. In the remaining 7, chronic appendicitis was the postoperative diagnosis.

The reaction to such a finding, as explanatory of a duodenal ulcer history, will depend on the individual to whom it is presented. The comment "Thank God for the appendix" may not be altogether unwarranted. It is only fair to state, however, that in each of the present instances there was found some gross evidence of pathology in the surgeon's friend in the right lower quadrant, and in addition, the laboratory staff reported chronic appendicitis. Moreover, in all the patients but the unfortunate neurasthenic, definite temporary improvement, at least, was observed following appendicectomy.

Unquestionably, we are operating year by year on fewer duodenal ulcers. The characteristic history and apparently positive Roentgen ray findings (such as were obtained in the cases here reported) are tempting us less and less to explore the abdomen. Rather are these patients being submitted to medical care and, unless obstructive lesions exist or develop, are being cured over and over again. Also, there is no doubt that the interpretation of the careful Roentgen ray investigation, to which all duodenal suspects are subjected, is gaining in accuracy and precision. The diminishing diagnostic error in this group, I believe, depends upon these two factors.

An entirely different situation exists in respect to duodenal ulcers which perforate. Here the emergency is acute, and early surgical intervention imperative. During this same 3-year period

the diagnosis of perforated duodenal ulcer was made 19 times, 6 times (31.5%) falsely. In nearly a third of the cases, therefore, in the presence of an acute abdominal emergency, perforated duodenal ulcer was fallaciously determined upon as the cause of the trouble. This is a fair indication of the attitude of the surgeon toward this grave emergency, and of its prominence in his mind as something demanding operation. He would rather be wrong many times in his diagnosis than to risk withholding needed aid in one such case.

Of the 6 errors recorded, 3 cases proved to be acute cholecystitis with cholelithiasis, 1 was a volvulus of the intestine with resulting gangrene, 1 was a perforation of a carcinoma of the sigmoid, and 1 an angina or coronary occlusion. This last mentioned patient gave a surprisingly accurate clinical picture of ulcer perforation, presenting, following his acute onset of abdominal pain, a striking rigidity of the abdomen coupled with exquisite tenderness. Our entire staff saw him, and all agreed in the necessity for exploration. The result was a fatality. The other 5 cases really merited surgical intervention although the diagnosis was wrong.

We have found the Roentgen ray a very valuable help in the necessarily hurried diagnosis of duodenal perforations. The subdiaphragmatic gas bubble which the examination frequently reveals is almost pathognomonic. Still, where this is not found, where liver dullness is not obliterated, we must still explore if the history and physical findings are typical. It is comforting to realize that the acute abdominal emergencies which may simulate the perforated ulcer—volvulus or other acute obstruction, perforation in some other portion of the intestine, fulminating cholecystitis with or without perforation, acute pancreatitis—all demand surgical aid. Were we able to elicit a careful history from these patients, a thing rarely possible in their distress, we might, perhaps, be able to eliminate some of the errors referable to acute cholecystitis. A history of previous attacks, suggesting cholecystitis, might put us on our guard as to diagnosis, but should not deter us from operating.

Miscellaneous. Of miscellaneous errors of diagnosis, not falling in any of these major groups, there were 29 in 3 years. These will not be discussed at length, and only the more interesting mentioned as indicative of the occasional vagaries of the surgical mind, or to point out some pitfall which may in the future be avoided.

One perinephritic abscess proved to be appendiceal abscess—a high retrocecal appendix accounted for the error. One appendiceal abscess proved to be an abscess of the kidney—a ptosed kidney felt as a tender mass in the flare of the ilium caused this one. Two hemorrhoids proved to be carcinomas of the rectum—we are sigmoidoscoping all our hemorrhoid cases now. One acute intestinal obstruction of unknown origin was caused by an inflamed Meckel's diverticulum. Two carcinomas of the stomach proved to be benign

gastric ulcers: often a difficult differential diagnosis, even at operation.

One megacolon proved to be carcinoma of the rectosigmoid. The dilatation of the gut was secondary to a low obstruction which, as may happen, was not visualized because it lay behind sigmoid coils. One carcinoma of the transverse colon proved to be chronic cholecystitis with cholelithiasis. The colon was kinked and distorted by adhesions, simulating neoplasm.

Summary. Total cases operated upon, 2340; total diagnostic errors, 110; percentage of errors, 4.6.

This catalogue of errors of diagnosis is presented merely as a record of clinical experience. What has been learned by this experience will, we believe, serve as a guide for the benefit of future patients. There is, it is felt, a real value in occasional analysis of diagnostic error both for the institution and for the individual surgeon.

BACILLARY DYSENTERY IN CALIFORNIA.

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Bacillary dysentery is an example of a so-called tropical disease which has a cosmopolitan distribution. The infection may lie dormant in the intestine without symptoms until the clinical disease is aroused by some intercurrent agent. When the incubation period exceeds 1 to 7 days, this is usually the case. The onset thus may be precipitated by some unrelated infection, by indigestion, chilling or fatigue. The onset is usually sudden, with variable fever, and with much increased pain and toxemia in warm climates and with the presence of Shiga strains of bacilli. The watery diarrhea soon becomes dysenteric and is accompanied by abdominal pain, prostration, vomiting and characteristic stools. The severity is influenced largely by the type of bacilli. The Flexner strains are milder and more common in California, and the Shiga type more severe and less frequent.

Pathology. A toxin is produced which causes a diffused catarrhal inflammation of the colon, in more severe forms going on to ulceration and necrosis of the mucosa and the production of a typical exudate. The inflammatory process is largely limited to the colon but may extend above the ileocecal valve. The bacilli rarely reach the mesenteric glands and do not otherwise leave the intestinal tract. They are not found, therefore, in the urine. In early stages and in mild cases, there is much stringy mucus and so-called snail-track

ulcers of the mucosa. The process is most intense in the rectum and distal colon, tending to spread upward.

In severe cases the inflammation intensifies to a necrosis, which may go as deep as the muscularis and gives rise to a purple-green diphtheritic membrane. In lighter cases, where discrete ulcers are present, the intervening mucosa is also inflamed, and ulcers tend to be transverse to the intestinal axis, have dirty sloughs in their bases and often there are submucosal connections between them. These ulcers are prone to outlast the acute infection, probably, as in the case of amebic ulcers, because of secondary bacterial invasion. The intestinal wall is not thickened as in the case of amebic colitis. Bacillary dysentery may lead to a chronic state in two forms. The first is accompanied by a persistence of dysentery bacilli, often difficult to culture, and by a frequent positive agglutination reaction in the blood. The second is a form of chronic ulcerative colitis most difficult to cure and an entity in itself. Further toxic effects are seen in the anterior horn cells, and in the production of fever, prostration and complications.

Complications include primarily arthritis, which is more common in rheumatic patients. Neuritis is not uncommon, especially in Asiatics, and may be a result of associated vitamin B deficiency. Conjunctivitis, iritis, otitis and myocarditis are seen. In young children and old people, bacillary dysentery is often a serious and dangerous infection. Much of so-called summer diarrhea is due to dysentery bacilli. Even in adults, typical dysentery is not always present, and the clinical picture may consist of a diarrhea of varying severity with more or less fever.

Diagnosis. "In no disease is the laboratory diagnosis of more value than in this. In fact, many cases can only be diagnosed by laboratory means, and it is always a necessary method of establishing the diagnosis, even under epidemic conditions. It is well to remember that the stools of bacillary dysentery are really an inflammatory exudate. Thus they show the characteristic sticky gelatinous mucus, with red cells often in rouleaux, numerous pus cells and desquamated epithelial cells, few bacteria, little odor and numerous macrophage cells which are large endothelial cells resembling amebæ but with no motility. The toxic course with a sudden onset, and the extreme frequency and susceptibility in children are to be noted."[1] Fecal elements are largely or entirely absent from the stool.

The first procedure in diagnosis is immediate, fresh examination of an unstained smear from the stool. This shows the characteristics noted above and, in the presence of characteristic clinical picture, is diagnostic. However, in all cases, this direct examination should be supplemented at once by bacterial culture on eosin and methylene

[1] Reed, A. C.: Tropical Medicine in the United States, Philadelphia, J. B. Lippincott Company, p. 118, 1930.

blue media for the dysentery bacillus group. Positive cultures are identified by agglutination and sugar fermentation tests. These procedures are to be left to the bacteriologist. It is the part of the clinician to see that certain definite requirements are met in making the culture. The tubes preferably should be inoculated from a freshly passed specimen and, at the latest, within 6, and preferably 2, hours after its passage. The media should be kept warm until placed in the incubator.

In fresh smears, it is to be noted that bacillary dysentery easily activates an infestation of Endamœba coli and is often followed by the appearance of intestinal flagellates. These should not divert attention from the main issue, which is the presence of dysentery bacilli. *E. histolytica* is less common in association with dysentery bacilli, and if very active amebæ, containing red blood cells, are numerous on the first day, there is less chance of the condition being a bacillary dysentery. Stool smears and cultures must be made at the earliest possible time. It is important to determine the strain of bacilli present, in order that the prognosis can be estimated and in order that treatment may be more highly specific.

After direct stool examination and culture, blood serum agglutination should be done in a competent laboratory against the several Flexner, and the Shiga and Sonne strains of bacilli. After the first 6 days, and in chronic and convalescent cases, agglutination is of paramount value.

Sigmoidoscopic examination is not desirable as a routine, is apt to be painful and may even aggravate symptoms. In chronic cases, the sigmoidoscope is invaluable.

Means of Spread. Transfer of dysentery bacilli is from man to man by mechanical or passive conveyance only. There is no specific or necessary vector and no intermediate or reservoir host except man. "The disease spreads from infection directly from patients, rarely from healthy carriers, and commonly from relapsing cases of chronic dysentery where bacilli are shed at irregular intervals. The bacilli may be on contaminated door knobs, latrine seats, fomites, etc., and thence pass to hands, to mouth, or to food or water and thus to mouth. Attendants on a patient are very apt to be infected because of the frequent, sometimes almost continuous stools, the sticky gelatinous nature of the passages, and the ease with which hands and fomites become infected. The danger from latrines used by mild or early cases is equally great. The bacilli are abundantly carried by the house-fly, almost certainly in desiccated form by dust, and contaminated food and fingers play the same rôle as in amebiasis and the typhoids. No age is exempt, but small children are particularly prone to infection. The bacilli are easily killed outside the body, especially by sunlight, so that in water exposed to sunlight they rapidly die, while in cool, shaded water they may survive several weeks. They are easily destroyed

by dilute antiseptics.[1] They die in low acid reactions. Thus their production of lactic acid in mucous flakes leads to their rapid disappearance in stool specimens.

Treatment. 1. Initial treatment should consist of bed rest and one dose of castor oil. Diet should be liquid or very soft, containing gruels, jellies, gelatins, beef tea, rice or barley water, arrowroot or sago puddings, and avoiding milk. L. L. Stanley advises feeding 2 ounces per day of dried whey powder in solution. Feedings should be at 2-hour intervals, and the food warm.

2. Regular inspection, at least daily, should be made of the stools, which are an important guide for treatment and for prognosis.

3. In more severe cases, and those not clearing at once with the treatment noted, and where fever is much in evidence, specific polyvalent antiserum should be given, in large and repeated doses, intravenously; 200 cc. of the appropriate serum may be repeated according to indications of fever, number of stools, abdominal pain and pulse. This should be associated with intravenous glucose. The action is antitoxic and, therefore, the effect is less curative as necrosis increases in the colon. Due precautions must be observed for serum sensitivity. Intramuscular injection is less desirable. Small children may be treated intraperitoneally or by rectum.

4. The well-tried sodium sulphate treatment is still to be recommended, in conjunction with the other methods indicated. Sodium sulphate is given in 4-gm. doses in water each 2 hours for 2 days, allowing 6 hours at night for sleep, if possible. After this, the same dose is given each 4 hours until the stools become feculent. In children, castor oil may be given in the same dosage and manner.

5. Pain is best relieved by external heat, absolute bed rest and combinations of belladonna, codein and chloral hydrate. Bismuth subcarbonate in teaspoon doses, 4 times daily, is often of great assistance. Opium is to be avoided.

6. Bacteriophage is worth using, especially in Shiga strain infections. It should be autogenous, if possible. Its actual value is still under debate.

7. Personal hygiene of nurses and attendants is extremely important. The frequent, sticky and mucoid stools easily contaminate linen and hands. It is dangerous to put the fingers in the mouth and frequent washing is necessary. Excreta and linen must be disinfected with crude cresol or phenol, or by boiling. The patient must be isolated and quarantine ought to be maintained until 3 negative stool cultures are obtained over a period of 2 weeks.

Chronic Bacillary Dysentery. Chronic bacillary dysentery merges gradually into chronic ulcerative colitis. Many cases diagnosed "chronic ulcerative colitis" are really chronic bacillary dysentery. The diagnosis and treatment are difficult. This status in endemic areas is often a precursor of sprue.

Incidence and Epidemiology in California. Since 1916, official

[1] Reed, A. C.: Tropical Medicine in the United States, Philadelphia, J. B. Lippincott Company, p. 113, 1930.

records show the presence of bacillary dysentery in California in sufficient quantity to constitute a definite and constant endemic distribution. Most of the cases have been reported in groups, the larger of these being institutional epidemics. Two observations are of practical aid in this connection: (1) Isolated or first cases need much better and earlier recognition in order to prevent spread into local groups or epidemics. (2) The problem of control of endemic sources needs intensive study. One wonders what the actual morbidity may be in proportion to each 100 cases reported.

The character of the California incidence reported makes of primary importance the immediate isolation of early suspicious cases and makes extremely urgent the rigid control of food handlers, especially in institutions and public restaurants. Undoubtedly, infected food handlers' direct contact with patients represents the chief and possibly only means of spread. Two points of attack need careful attention. In the first case, physicians need education in the safe and proper technique of caring for diarrheal cases in the home and also in the hygiene of food handling in the home. This information should be passed on to mothers and housewives. It should include especially detailed instruction in the importance of contaminated hands in relation to food and the importance of keeping fingers and mouth always apart. In the second case, the sanitary care of patients with diarrhea needs detailed instruction. Better control and examination of food handlers in institutions and restaurants is a crying need and demands attention. Rural districts need inspection and control of water supply, sewage disposal and abolition of open privies.

The chart of incidence of bacillary dysentery in California, appearing below, was prepared by Miss Ida M. Stevens, Supervising Morbidity Statistician of the California State Department of Public Health. Miss Stevens states (personal letter) that "In 1917, the 12 cases of Hiss-Russell-Y type occurred in an Oakland Hospital and the records for the county as a whole are not available. The same is true of Orange County in 1918—a group of 5 cases, Shiga type, were investigated by our epidemiologist, but our morbidity records from 1918 do not include the distribution by counties. This is likewise true of Napa County, in 1916, in which there were 400 cases of H. R. Y type. I might explain that reporting has improved in the last few years. Also there are more laboratory facilities available in the southern part of the state—this might

TABLE 1.—TOTAL CASES OF BACILLARY DYSENTERY REPORTED TO STATE BOARD OF HEALTH FROM CALIFORNIA.

1917	12	1925	62
1918	5	1926	277
1919	0	1927	148
1920	119	1928	57
1921	19	1929	1168
1922	9	1930	113
1923	66	1931	150
1924	45	1932	302

TABLE 2.—CALIFORNIA STATE DEPARTMENT OF PUBLIC HEALTH. CASES OF BACILLARY DYSENTERY.

County.	Year.	Total cases bac. dysentery Reported.	Types.		
			Shiga.	Flexner.	H. R. Y.
Alameda	1917		..	..	12
	1920	37	..	..	35
	1921	9	..	4	
	1922	5	..	..	5
	1925	2	..	1	
	1926	4	1	1	1
	1930	4	..	1	1
	1932	4	..	1	
Butte	1927	1	..	1	
Colusa	1930	4	..	4	
	1931	1	..	..	1
Contra Costa	1930	6	..	6	
El Dorado	1929	1	..	..	1
Fresno	1931	4	..	1	
Imperial	1928	1	..	1	
	1932	3	..	1	
Kings	1921	1	..	1	
	1923	2	..	1	
	1927	7	..	..	7
Lake	1932	16	..	16	
Los Angeles	1920	47	6		
	1923	47	..	1	
	1924	41	..	4	
	1925	58	..	2	
	1928	43	14	10	1
	1929	68	..	26	20
	1930	90	4	12	
	1931	141	3	18	
	1932	200	4	40	
Madera	1930	1	..	1	
	1932	2	..	1	
Marin	1926	27	..	26	
	1927	138	..	138	
	1929	947	..	946	
	1930	1	..	1	
Mendocino	1923	1	..	1	
Merced	1931	1	..	1	
Monterey	1927	1	..	..	1
Napa	1916	..	..	..	400
	1929	134	..	134	
	1932	17	..	..	17
Orange	1918	..	5		
	1923	5	1		
Placer	1929	5	..	..	5
Riverside	1928	2	..	2	
	1932	3	1		
Sacramento	1929	1	1		
	1930	6	2	4	
	1932	4	..	1	1
San Bernardino	1929	12	5		
San Diego	1923	13	..	12	
San Francisco	1922	4	..	1	
	1923	2	..	..	1
	1932	8	1	4	
San Joaquin	1921	9	..	8	
	1931	1	..	1	
San Luis Obispo	1925	2	1		
San Mateo	1928	11	..	9	
	1932	1	1		
Santa Clara	1932	10	3		
Sonoma	1927	1	..	1	
	1932	3	1		
Stanislaus	1931	2	1		
Sutter	1930	1	..	1	
Tulare	1926	243	..	..	237
Tahoe District	1926	3	..	3	
Tuolumne	1924	4			

account for the apparent increase of cases in that area." It is to be noted that the high incidence in Marin County, in 1927 and 1929, was due to epidemics in San Quentin prison.

Case Reports. CASE 1.—Mrs. C. H. (Kindness of Dr. F. E. Stiles.) A housewife, aged 31, was taken ill on October 30, 1932, with a sudden intense diarrhea, accompanied by fever, abdominal pain and prostration. In 3 days, blood and mucus appeared in the stools. On November 11, 12 days after onset, acute arthritis developed in certain phalanges, later involving ankles, knees and other joints. The arthritis was migratory. Stool culture on November 12 was negative for dysentery bacilli. The blood agglutination was positive for the Shiga group. Stool smears showed excessive pus, mucus, epithelial and cellular elements and débris. On November 6, she contracted an upper respiratory infection, complicated by acute conjunctivitis and iritis. Treatment was symptomatic until November 12, when she received 50 cc. Shiga antiserum intramuscularly, with immediate and permanent cure of the arthritis and residual colitis. Convalescence was uninterrupted and she was dismissed in good health on December 6. The blood count on the 11th day was as follows: Hemoglobin (Sahli), 61 per cent; red cells, 3,150,000; white cells, 12,800; polymorphonuclears, 81 per cent. Urine was normal. The special nurse in charge of the patient showed negative stool culture and agglutination tests.

CASE 2.—Mr. L. H. Teacher, aged 31, son of Mrs. J. H. (Case 3), with whom he made his home, was taken ill 4 days after onset of his mother's illness, with severe diarrhea, lasting 1 week. He did not note the presence of fever. The stools were free of blood. There was no nausea, arthritis or other complication, but considerable abdominal soreness. After 1 week, recovery took place without treatment. He was first seen and examined on the 20th day after onset, and 12 days after cessation of diarrhea. Physical examination was not remarkable. The abdomen was relaxed, and free of tenderness or abnormal masses.

The blood count was as follows: Hemoglobin (Sahli), 79 per cent; red cells, 4,340,000; white cells, 10,480; with polymorphonuclears, 68 per cent; lymphocytes, 24 per cent; mononuclears, 5 per cent; eosinophils, 3 per cent.

Stool culture for dysentery bacillus group was negative. The stools were free of any parasites. Blood gave strong Shiga agglutination reaction.

CASE 3.—Mr. J. H. Housewife, aged 64, began to have diarrhea on November 1, after she had taken care of her daughter for 3 days (Case 1). Two days later, blood appeared in the stools and there was some vomiting. The diarrhea rapidly became dysenteric, was attended by fever, prostration, tenesmus and abdominal pain. Death occurred in shock on November 21.

Previous history was of obesity and chronic cholecystitis with stones.

Examination showed marked obesity, moderate abdominal tenderness and prostration.

Laboratory findings were not available when she was first seen on November 10. At that time, direct inspection of a fresh stool showed little fecal material, large proportion of whitish, translucent flaky mucus giving a milky appearance, much mixed blood, extreme viscidity, and lack of fecal odor. Direct microscopic examination showed enormous numbers of pus cells, macrophages and scattered red cells. This led to a tentative diagnosis of bacillary dysentery. Stool cultures, made at once, were positive for B. dysenteriæ (Shiga), and there was a Shiga blood agglutination complete at 1 to 40 and partial at 1 to 80. B. dysenteriæ Hiss-Russell-Y and B. dysenteriæ Flexner were agglutinated at 1 to 160. Agglutinations were negative for B. typhosus, B. paratyphosus A and B, B. enteritidis and B. abortus.

Treatment was symptomatic; usual dietary and supportive measures, and colon irrigations with acriflavin. On November 11, 100 cc. Lederle

polyvalent dysentery serum was given in the muscle. On November 14, this was repeated. On November 16, 100 cc. were given in the vein with glucose, and this was repeated on November 17. Glucose was given repeatedly in the vein. On November 20, the patient went into shock, and died on November 21, after a progressive increase of toxemia. Post-mortem examination showed a chronic cholecystitis with numerous stones and a generalized peritonitis. There was extensive ulcerative colitis. Fever chart is appended (Chart I).

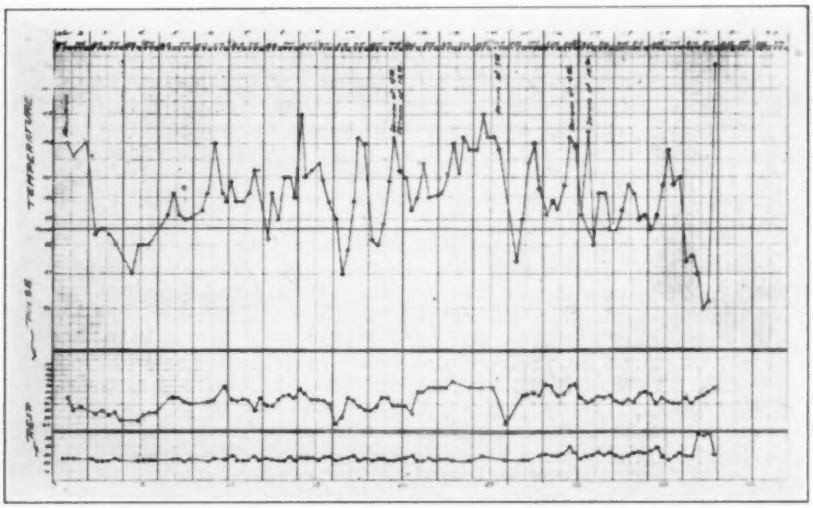

CHART. I.—Temperature chart of bacillary dysentery, Case 3.

Conclusions. 1. Bacillary dysentery is widespread in California on an endemic basis, from which institutional and local epidemics easily and frequently arise.

2. Early recognition is necessary for control.

3. Early treatment, especially in severe cases, is essential and demands early diagnosis.

4. Control depends chiefly on personal hygiene, non-infected food handlers and housewives, proper care of clinical cases, clean water supply and safe sewage disposal.

AGRANULOCYTOSIS AND ACUTE LEUKEMIA.

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ANGINA agranulocytica of Schultz,[1] agranulocytosis of Friedemann,[2] malignant neutropenia of Schilling,[3] pernicious leukopenia of Fitz-Hugh and Krumbhaar[4] and other terms appear to be, to a

superficial observer, antithetic terms to acute leukemia. That is correct if we accept the frequently expressed opinion that agranulocytosis is largely due to an aplastic condition of the bone marrow, whereas the acute leukemia involves a process similar to that of chronic leukemia, but acute in its course. However, this is not the true situation. Let us analyze the two forms in order to find in what points they differ and where they are similar. For agranulocytosis or malignant neutropenia we will indicate a syndrome that by virtue of its fairly constant behavior, although not constituting a definite clinical, pathologic or even hematologic entity, stands out fairly well and is not to be confused with other forms of neutropenia occurring as a temporary picture in a group of well-known diseases, such as typhoid fever, epidemic parotitis, influenza, pappataci fever, Malta fever, pernicious anemia, non-complicated chronic tuberculosis, very severe sepsis and in certain intoxications, such as benzol, gamma rays, mesothorium, Roentgen ray, trinitrotoluol, arsenical compounds, etc. The term acute leukemia is used, as it does not seem necessary to differentiate between myelogenous, lymphatic and monocytic forms. The question of the possible identity of the 3 forms is not relevant to the present topic. We wish also to emphasize that we are considering *manifestations* of the 2 diseases without regard to their bearing on the fundamental nature of the two conditions.

Let us consider the clinical course. It is similar in the two diseases. In both cases we have an obscure insidious onset, although apparently the symptoms develop suddenly. The course of both is characterized by septic manifestations with high fever, ulcerations of the mouth and intestinal tract, and rapidly downward course. Minor differences are found in the duration, which is, as a rule, shorter in single attacks of malignant neutropenia and somewhat longer in the acute leukemia. It is true that from the time that symptoms appear to the date of death, a number of cases of acute leukemia last only few weeks, sometimes a few days; but cases of such short duration are not common and, on the other hand, the blood changes characteristic of the disease may precede the terminal clinical picture for a considerable period of time. Splenic enlargement of moderate size is constant in acute leukemia and usually absent in agranulocytosis. Lymph-node enlargement is also more common in acute leukemia than in agranulocytosis, not taking in consideration the enlargement of cervical lymph nodes, secondary to mouth infection, which is common in both conditions. Another difference is that, whereas profound anemia is always present in acute leukemia, in agranulocytosis it usually develops somewhat later in the course of the disease. A tendency to hemorrhage is present in both conditions. Whereas recovery in acute leukemia is exceptional, a few of the patients of agranulocytosis appear to recover spontaneously. If, however, the cases of severe

neutropenia following the already mentioned intoxications are removed from the list, one will find that spontaneous recoveries from agranulocytosis are indeed rare. Clinically, therefore, it appears that there are no essential differences between the two forms.

Hematologically and pathologically the differences are less than one would imagine. The essential difference which might be suggested by the names and is maintained by some authorities is that in malignant neutropenia the bone marrow is aplastic, whereas in acute leukemia it is hyperplastic. This also is not a real difference, at least in the majority of cases. In several cases of agranulocytosis which I had occasion to see at the autopsy table, the bone marrow was grossly active, or even hyperactive, occasionally hemorrhagic and microscopically showed evidence of active multiplication of cells which showed oxidase granules, although many of them on smear and section did not show any mature granulations. The cells in question were mostly undifferentiated and immature myeloid cells. In fact, the bone marrow examination suggested strongly the picture seen in acute leukemia, the main difference being that, whereas in acute leukemia the undifferentiated cells and immature cells are produced in excess and released in the circulating blood, in agranulocytosis they are retained in the bone marrow. Nor is this the only example of variation in the mechanism of release of immature cells affecting a differentiation between related lesions of the hemopoietic system. Experimentally, Richter and McDowell[5] and Furth and Strumia[6] found that typical lymphatic leukemia, aleukemic leukemia and lymphosarcoma may be obtained in strains of susceptible mice from the inoculation of material from mice affected by chronic lymphoid leukemia, the difference between these forms probably being due to differences in the mechanism of release in the blood of the newly formed lymphocytic cells.

Fitz-Hugh and Krumbhaar[4] speak of a "maturation arrest." These authors noted in a case of agranulocytosis a state of marked hyperplasia of immature myeloid elements of bone marrow. In 2 other cases of agranulocytosis, immature myeloid cells were present in the bone marrow in increased numbers. These authors also emphasize the necessity of considering the bone marrow condition for the proper interpretation of the neutropenic state, and mention the similarities to pernicious anemia.

Custer[7] thus expresses himself: "I believe that one should differentiate strictly between those neutropenias of secondary nature (symptomatic agranulocytosis) and those of the primary type (essential agranulocytosis, Schultz's syndrome), both on clinical and histopathologic grounds. With regard to the latter, I have found in all cases that fit the clinical features of the primary type a rather consistent bone marrow picture. The marrow is always hyperplastic, the degree depending on the duration of illness; the increase in cellularity is largely confined to the granulocyte progenitors,

shared to slight degree by the erythropoietic series. More specifically, the hyperplasia is of myeloblasts and promyelocytes; rarely is a fully granulated neutrophilic myelocyte found (in 1 case I searched through many sections of 5 bones without finding a single granulated cell of the neutrophil type). Beyond the promyelocyte, one finds degenerating forms (ghost cells) that from their nuclear remnants are often identified as belonging to the series in question. Some of the cases show focal areas of necrosis, in the periphery of which there is a lymphocyte and plasmocyte reaction, sometimes extensive enough to completely cover the necrotic center."

Anatomically, from an examination of a large number of autopsies, I have constantly found in the bone marrow of acute leukemia a picture very similar indeed, although, as a rule, more severe than that found in agranulocytosis. The fundamental difference is that, whereas in agranulocytosis there is an arrest of maturation of cells without release of these cells in the circulating blood, in acute leukemia these immature cells are released into the blood. This difference might be minimized if one considers that in agranulocytosis one always finds in circulation a small number of highly immature granulocytic cells and that a large number of shadow cells occur in both diseases. Another important difference, possibly related to the previous one, is that, whereas in acute leukemia there are foci of cellular infiltration in other organs of the body, in agranulocytosis one does not find such foci. In both diseases there is a constant severe deficiency of mature granulocytic cells in circulation. This deficiency is never present in chronic myelogenous leukemia, and in chronic lymphatic leukemia it occurs only occasionally in the very last period of the disease. Essentially, therefore, in both agranulocytosis and acute leukemia the clinical manifestations of sepsis are probably secondary to a disappearance of the protective function of the neutrophilic cells from the circulating blood. Another strong point of resemblance is that, in both agranulocytosis and acute leukemia, degenerative lesions of the bone marrow occur very commonly. Finally, I will mention the fact that, in a number of cases of acute leukemia, the typical hematologic picture is preceded by a picture of neutropenia.

The purpose of this paper is to present 3 cases of acute blood dyscrasias that presented at one period or another of their course alternatively the hematologic features of acute leukemia and those of agranulocytosis. Schenck and Pepper[8] seem to have been dealing with a similar case in their presentation in 1926 of a case of acute lymphoblastic leukemia with remission characterized by neutropenia. These authors remark on the confusion in differential diagnosis between acute leukemia and infectious mononucleosis. This confusion is partly due to the chaotic nomenclature of blood cells, but much more so to the improper knowledge of blood morphology on the part of those who examine the blood films. I have

for many years adopted, with minor modifications, Ferrata's[14] blood-cell classification and nomenclature, which is similar to that of Pappenheim, and consider it one of the most satisfactory. Borchard,[9] in 1930, presented a case of agranulocytosis in a female patient in which the picture changed to a typical form of acute myeloblastic leukemia followed by death. Lindemann,[10] in 1930, emphasized the similarity between 3 cases, 1 of glandular fever with mouth infection and recovery, 1 of typical acute lymphatic leukemia, with death, and 1 of severe agranulocytosis, also terminating in death. In 1931, Wolff[11] reported 2 fatal cases in a brother and sister, 1 of agranulocytosis, the other of myeloblastic leukemia, as forms of reaction to the same infection. Such cases appear to support the thought that in both forms we are perhaps dealing with a pre-existing congenital or acquired deficiency of the bone marrow, combined with an intercurrent non-specific toxemia, probably infectious, or perhaps with a phenomenon of a hypersensibility to certain substances. Wolff concludes from his own cases, and from the literature reports, that agranulocytosis, aplastic anemia, aleukia (Frank) and the acute leukemias do not constitute independent diseases, but represent abnormal reactions to a septic infection, based upon a constitutional inferiority of the blood organs. Burkens,[12] in 1931, reported a fatal case of agranulocytosis followed by acute leukemia in a girl, aged 16, the attack of acute lymphatic leukemia occurring 1 year after the attack of agranulocytosis. He speaks similarly of constitutional inferiority of the regulating mechanism of hemopoiesis, revealing itself first with an agranulocytic picture and later with a fatal acute leukemia. More recently, Fitz-Hugh and Comroe,[13] reviewing 18 cases of agranulocytosis, report that necropsy study in 9 cases has shown in 6 moderate or intense hyperplasia of the immature myeloid elements, in 2 a normal picture and in only 1 (a case not examined by the authors) scarcity of myeloid elements. Müller and Spröhnle[15] described a case of hypochromic anemia and leukopenia with few immature leukocytes in the circulating blood in which suddenly a typical picture of acute leukemia appeared.

Case Reports. CASE 1.—J. T., a white male, aged 21, was admitted to the Misericordia Hospital on August 17, 1931 (service of Dr. J. A. Sweeney). About 10 weeks previously he first complained of shortness of breath on exertion and pains in the back. Two weeks prior to admission, dizziness and headache appeared. Three days before admission, a tooth abscess developed. On admission the patient showed paleness of skin and mucosa, few petechiæ over the abdomen and left arm, moderate enlargement of the cervical, axillary and inguinal lymph nodes, slight enlargement of the spleen which was palpable below the costal margin, slight oozing of blood from the gums with stomatitis and a suppurative process about the lower right 1st and 2d molars with a fistula; a blowing systolic murmur of the heart. The temperature was irregular, subfebrile most of the time, with a maximum of 103° F. The blood examination on admission showed: coagulation time, 4½ min.; bleeding time, 6½ min.; hemoglobin, 3.35 gm.;

erythrocytes, 1,160,000; leukocytes, 36,300. The differential count showed: hemocytoblasts and hemohistioblasts (undifferentiated cells), 84%; promyelocytes, 2; metamyelocytes, 1; prolymphocytes, 3; lymphocytes, 7; Türck cells, 3%. A large percentage of the undifferentiated cells showed oxidase granules. The diagnosis of acute leukemia of the myelogenous type appears well justified.

The clinical condition and leukocytic picture went on almost unchanged, save for variation in the number of the leukocytes, from a minimum of 6700 to a maximum of 72,000, for a little over a month. During this period the patient received repeated blood transfusions at fairly even intervals which did not apparently alter either the course or the blood picture. At the end of this period, or about September 15, the leukocytes in the circulating blood rapidly declined in number until they reached figures below 1000 per cmm. Along with the drop in the total white cell count a very interesting change took place in the leukocytic formula, that is, the progressive disappearance of the myeloid elements, both mature and immature. The blood picture on October 5 is typical of the agranulocytic period: hemoglobin, 7.3 gm.; erythrocytes, 1,960,000; leukocytes, 550. Differential count: hemohistioblasts, 1%; rod nuclears, 1; neutrophils, 1; prolymphocytes, 3; lymphocytes, 94%. This granulopenic phase went on for about 1 month. During this period the leukocytes were as low as 400 per cmm. and seldom above 1000. The anemia improved somewhat, and so did the clinical condition of the patient. About November 3, the undifferentiated myeloid cells reappeared in the blood stream, and in 3 weeks, from a count of 2100 leukocytes per cmm., a maximum of 430,000 was reached.

The blood picture at the end of the disease (November 18) was again that of a typical acute leukemia with 240,000 leukocytes and the following differential count: hemohistioblasts and hemocytoblasts (undifferentiated cells), 41%; myeloblasts, 40; promyelocytes, 4; myelocytes, 1; polymorphonuclears, 2; lymphoblasts, 3; lymphocytes, 5; Türck cells, 2; undetermined, 2%. It is interesting to note that at this stage few of the undifferentiated cells were oxidase positive, although many were unquestionably of myeloblastic nature. This phenomenon has been observed by me in other cases of acute myelogenous leukemia. Under such conditions, even typical neutrophils do not show oxidase granules. During the whole course of the disease, the platelets were very low, varying between 25,000 and 70,000. During the last few days of life an autoagglutination of the red cells *in vitro* took place, rendering red cell counts impossible.

An analysis of the behavior of the differential count shows that with the decrease of the undifferentiated cells there is a sharp increase, first of the immature granulocytes, then of the mature granulocytes, as if the maturation of these cells had become progressively possible for a short period of time. The same phenomenon occurred, but reversed and somewhat less strikingly during the reappearance of the undifferentiated cells. The patient died with symptoms of cerebral hemorrhage on November 20, about 5½ months after the onset of the first symptoms and about 3 months after the disease was diagnosed. Chart I summarizes the variations of the hematologic picture.

Case Summary. We have, therefore, a case of acute leukemia of the myelogenous type, with a period of leukopenia and granulopenia lasting over a month, with clinical improvement, followed by a rapid and fatal return of the leukemic picture.

Case 2.—E. Y., a school girl, aged 9, was first seen by me on October 18, 1927, the history being that from March the child had noticed petechiæ all over the body and black and blue marks after slight injuries. About May, bleeding from the nose occurred. During this period the patient had been treated with repeated blood transfusions. There had been all

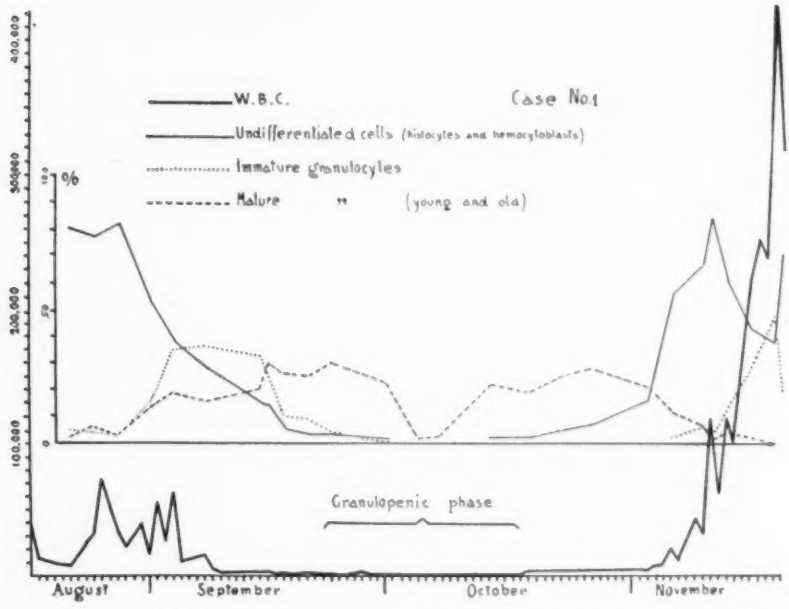

CHART I.—Note the typical picture of acute leukemia (granulocytic) at the beginning and end of diseases, with a striking intermediate granulopenic phase.

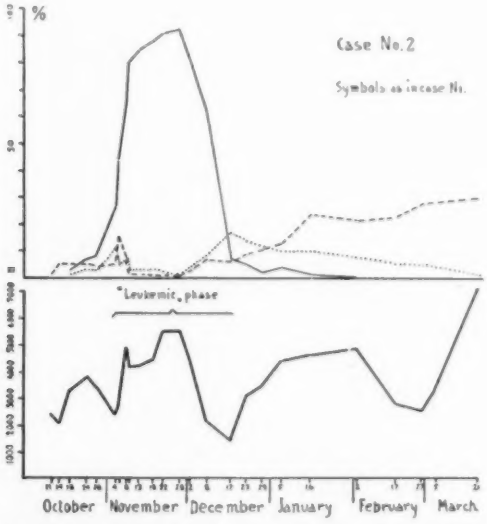

CHART II.—An early granulopenic phase is followed by a typical acute leukemic picture (lymphoblastic). This is followed by a second neutropenic phase from which the patient slowly improves.

along a severe mouth infection which in July rapidly spread with formation of fetid sores all over the mouth and finally sloughing of 1 tonsil. The temperature had been intermittently high. The hemoglobin content, the red cells and the platelet count were constantly low. On October 11 the blood examination showed bleeding time of over 15 min., coagulation time 4 min.; platelets, 33,000; hemoglobin, 9.2 gm.; red blood cells, 1,785,000; white blood cells, 2400; neutrophils, 1%; basophils, 2; prolymphocytes, 4; lymphocytes, 92; monocytes, 1%—a picture, therefore, of anemia and leukopenia with great decrease in the total number of granulocytic cells, but practically no change in the lymphocytic series. The diagnosis of agranulocytosis was made.

On or about November 4, a distinct change occurred in the differential count. There was a rapid and continuous increase in the number of the undifferentiated cells which finally reached the total figures of over 90%. There was at the same time a slight increase of the total white cell count. This phase, having hematologically all the characteristics of an acute leukemia, lasted about 1 month. During the acme of this period, on December 28, the differential count showed 92% hemocytoblasts, 1% promyelocytes, 1% rod nuclears (young neutrophils) and 6% lymphocytes, with a total leukocyte count of 5600. The undifferentiated cells at the end of the leukemic period disappeared as rapidly as they had appeared, and there was again a picture of leukopenia with granulopenia which, however, began slowly to improve (Chart II). The improvement extended over a period of 3 years. The patient was treated with a very large number of blood transfusions and injections of fresh serum. The child is at present living and apparently well, but still has a low white cell count, ranging from 4000 to 5000, with a relative lymphocytosis and a mild absolute granulopenia. From the table it can be seen that during the period of increase and decrease of the undifferentiated cells, an increase of both mature and immature granulocytic cells occurred. The majority of the undifferentiated cells (hemocytoblasts) showed positive oxidase reaction.

Case Summary. The second case shows a rather long-standing granulopenia with a sudden change of the blood picture to one of acute leukemia of the myelogenous type. This picture lasted about 1 month and eventually disappeared, the agranulocytic picture then returning, and the patient slowly improved. The improvement has lasted during the period of observation up to date.

Case 3.—Z. F., a white male, aged 5, first came to my observation on October 20, 1931. The child had been ill for about 1 month, with irregular high fever, abdominal pains, diarrhea with bloody stools and mucus. On the first examination, the child showed pallor, temperature ranging from 103° to 104° F. with daily remissions, diffuse mouth infection, rapid pulse, a systolic murmur and muffled heart sounds. Hospitalization for study was advised, and on November 7 the child was admitted to the Pediatric Service of the Mt. Sinai Hospital (Dr. Harry Lowenburg). The physical condition at the time of admission had not changed considerably since the previous examination. In addition the lips were swollen, fissured and bleeding. The posterior cervical glands were larger than normal and tender to the touch. The lungs were impaired at both bases with fine crackling râles. The Roentgen ray showed marked infiltration suggesting bronchopneumonia and evidence of pericardial effusion. The systolic murmur was still present, but disappeared 10 days later, and the heart sounds became more distinct. The child was treated with 4 blood transfusions and discharged improved on December 3, 1931. The temperature had been between 99° and 105° F. for several days, finally returning to normal. Smears from the gums showed many fusiform bacilli.

The patient was readmitted to the same institution 2 weeks later with fever and generalized lymphadenitis and enlargement of liver and spleen. Splenectomy was performed on January 21, 1932. The spleen weighed 500 gm., was moderately firm, deep purplish red in color with hyperplastic lymph follicles and a slightly thickened capsule. Microscopic examination gave the following result: The capsule was well preserved, normal in thickness. Outside of the capsule and adherent to it there was a thin layer of lymphocytic cells appearing in groups that continued to the spleen pedicle. Here the capsule appeared to be thoroughly infiltrated by lymphocytic cells. These lymphocytic cells, which form the bulk of the splenic tissue, were larger than the ordinary lymphocytes, the nuclear structure was much more delicate than that of the mature lymphocyte; they showed a number of nucleoli. The cytoplasm was relatively scanty and basophilic. These cells showed very numerous mitotic figures, and formed irregular, compact areas with almost complete loss of the normal splenic structure. There were a few well-preserved lymph follicles, which were, however, very greatly hyperplastic. This picture was in sharp contrast with that of chronic lymphatic leukemia, where the prevailing cell is the prolymphocyte (a small lymphocyte with a compact, very dark staining nucleus). The cell prevailing in the sections can be identified either with the lymphoblast or with the lymphoid hemocytoblast. It is the picture of an acute leukemia and not the picture of a chronic lymphatic leukemia. It is of very great interest to note that, although the picture offered by the spleen was surely that of acute leukemia, the typical leukemic changes in the blood were not as yet established and did not definitely appear until several weeks later. A similar behavior was found by Furth and Strumia[6] in susceptible mice inoculated with material from leukemic animals.

The temperature at this time was irregular, with febrile periods. The patient received numerous blood transfusions and was discharged on March 18, 1932. He was readmitted on April 4, when new glandular enlargement was detected in the axilla and in the groin. Child had at this time a septic temperature with elevations up to 105° F. He was treated again with repeated blood transfusions and discharged on April 15. The blood picture at this time was typically that of an acute lymphocytic leukemia.

After a period of 4 weeks of relative improvement at the Convalescent Home he was readmitted to the hospital for blood transfusion. During this period the temperature varied between 98° and 104° F., finally remaining normal for 4 days. He was discharged, only to be readmitted 4 days later because of distention of the abdomen and severe pains in the right upper quadrant. His temperature on this last admission was 100° F., and the liver larger than on previous occasions. Adenopathy was still present. A bilateral parotitis developed, with some bleeding from the mucous membrane of the lips and the left cheek. The temperature now varied between 98° and 105° F. The child died on July 5, 1932.

Clinical Summary. A five-year-old child acutely ill with septic temperature, generalized adenopathy, enlargement of the liver and spleen, mouth infection, occasional bleeding and occasional intercurrent infections of various organs (lungs, pericardium, parotid glands, intestinal canal). The blood picture is summarized in Table 1. In addition it should be stated that on several occasions there had been a moderately low platelet count (190,000 and less). The course of the disease could roughly be divided into 3 periods: The infectious period, from the time of the first observation up to about December 16; the granulopenic phase, from December 16 to about January 15; and thereafter to the end, the progressive leukemic phase.

The rapid course of the disease, the septic character, the relatively low

white cell count, with a large percentage of undifferentiated or highly immature cells during the leukemic period, fully justified the diagnosis of acute leukemia of the lymphocytic type. The oxidase stains done on several occasions always showed that the undifferentiated cells were oxidase negative.

The autopsy (Dr. D. Meranze) fully confirmed the diagnosis of acute leukemia. The body showed considerable emaciation. All lymph nodes of the body were greatly enlarged, particularly in the mediastinum, near the pancreas, and the mesentery. The lymph nodes appeared soft, fleshy, often hemorrhagic. Hemorrhages were present over the pericardium, in the liver, the kidneys, the stomach. Gross leukemic infiltration was present in the left kidney, which was greatly enlarged and weighed 140 gm. The bone marrow (femur) was hyperplastic. Microscopic examination (Strumia) showed:

Bone Marrow. Distinct hemopoietic hyperplasia, with very great reduction in number of mature granulocytic cells. There were very few erythro-

TABLE 1.—BLOOD FINDINGS IN CASE 3.

	October 20, 1931.	November 16, 1931.	March 7, 1932.	May 9, 1932.	June 7, 1932.
Hemoglobin (grams)	7.1	10.5	10.0	3.0	2.5
Red blood cells	2,500,000	3,070,000	2,520,000	1,000,000	880,000
White blood cells	4,800	3,200	20,800	71,300	4,500
Hemohistioblasts	....	....	....	0.6	....
Hemocytoblasts	....	....	1	0.4	13.5
Myeloblasts	....	1	....	....	0.5
Promyelocytes	....	2	....	0.2	....
Myelocytes	....	1	....	....	....
Metamyelocytes	1	4	....	....	....
Rod-nuclears	5	22	2	....	1.0
Neutrophilic polys.	1	20	2	0.2	0.5
Eosinophils	....	....	....	....	....
Basophils	....	1	....	....	....
Lymphoblasts	1	....	16	7.2	36.5
Prolymphocytes	5	17	14	90.4	28.0
Lymphocytes	87	32	65	0.8	12.0
Monocytes	....	....	....	....	0.5
Erythroblasts basophilic	....	....	....	....	1.5
Erythroblasts metachromatic	....	....	....	....	5.5
Erythroblasts eosinophilic	....	....	....	....	0.5

blastic foci. Most of the cells were large cells with relatively scanty cytoplasm, large vesicular nucleus with fine structure, basophilic cytoplasm and no granulations. Megakarocytes were very rare. Occasional edema. There were numerous mitotic figures and fairly numerous large cells fitting well the description of hemohistioblasts. Oxidase stain not carried out. The lesion could be summarized by saying that there was a distinct hyperplasia, with lack of mature myeloid cells, erythroblastic foci and megakaryocytes. The predominating cells were undifferentiated, very similar to those found infiltrating the other organs.

Lymph Nodes. The structure of the lymph node was entirely lost. There were extensive areas of hemorrhagic infiltration. The bulk of the tissue was formed of loose fibrillar tissue thoroughly infiltrated with relatively large cells, with basophilic cytoplasm. These cells appeared to be

of two distinct types. There were some with very scanty cytoplasm, compact, heavy stained nucleus with little or no structure (prolymphocytes). There were also a number of cells with more abundant cytoplasm, large vesicular nuclei, with a rather delicate structure and occasional nucleoli (lymphoblasts).

Liver. The liver tissue proper showed degenerative changes with granulation of the cell cytoplasm and generally poor nuclear stain. There was some dilatation of the central veins and surrounding capillaries with a small amount of hemosiderin deposit. The outstanding lesion, however, was the presence of bulky thick cellular infiltration which occurred regularly in the periphery of the lobules. The cellular infiltration was made up of cells mostly of the lymphocytic type, of the same two kinds as in the lymph nodes. Diagnosis: leukemic infiltration.

Kidney. Most glomeruli showed in the capsular space extensive serous exudate in the form of granular pink staining material. The tubular epithelium showed extensive degenerative process, the lumen being filled with the same granular material already mentioned. In addition there was extensive cellular infiltration, which occurred sometimes around the glomeruli, sometimes around and between the tubules. It was formed of lymphocytic cells, identical to those already described for other organs. There were also small areas of hemorrhages. Diagnosis: parenchymatous nephrosis; leukemic infiltration.

CASE SUMMARY. This case, somewhat more complex than the previous ones, is of very great interest because it shows a typical infectious picture with progressive depression of the granulocytic activity followed by an abnormal regeneration of the lymphocytic cells, with appearance in the circulation of a large number of undifferentiated and highly immature cells, and a typical clinical and postmortem picture of acute leukemia.

Summary and Conclusions. Evidence gathered from the clinical course, the hematologic picture and the anatomic lesions of the 2 diseases point to many similarities between agranulocytosis and acute leukemia. These similarities are made more striking by at least 6 reported cases of transition of one form into the other, 3 of which are presented in this paper. The essential disturbance dominating both pictures seems to be a defect in the bone marrow, whereby the immature parent cells become incapable of maturation, a disturbance perhaps based on a constitutional imperfection of the hemopoietic system, congenital or acquired, in both cases. The rôle played by intercurrent infections, toxemias or susceptibility to various substances may be the deciding factor in the development of the acute picture, though not necessarily a specific one. An essential difference between the 2 forms seems to be in the mechanism of release of the immature and undifferentiated cells into the circulating blood, a release which occurs in acute leukemias, but not in agranulocytosis.

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NEUTROPENIA DEVELOPING DURING AMIDOPYRIN MEDICATION.

With Report of 2 Cases.

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Amidopyrin has been used extensively in this clinic as an analgesic in the treatment of chronic arthritis. Schultz[1] reported that the drug had little, if any, toxicity; but 2 of the patients in our series developed neutropenia while taking it. In 1 case the association seems definite while, in the other, the relationship is suggestive but not conclusive. We were unable to find reference in the literature to the neutropenogenic action of amidopyrin. Hence the 2 following case reports:

Case 1.—A. M., white male, 48, admitted May 13, 1933. Had arthritis about 5 years. Ten months previous to admission two infected teeth were extracted and the tonsils were removed. The blood Wassermann reaction was negative. The remainder of the history and physical examination were unimportant. The blood count on admission was: R. B. C. 4,250,000, W. B. C. 10,000, polys. 68, lymph. 22, mono. 4, eos. 6%. Beginning May 13, 3 tablets each consisting of a combination of magnesium carbonate gr. iv and amidopyrin gr. iiss, were given daily until May 23. The dose was then increased to 4 tablets daily until June 6, when it was discontinued. The blood count was normal at that time. On June 10, amidopyrin gr. xv was given daily until June 17 when it was increased to gr. xx daily. This dose was continued until June 26 (a total of 285 gr. in 16 days) when the neutropenia was discovered (Table 1). At the time of the neutropenia, the patient felt quite well. There was no sore throat and no untoward symptoms were observed. The blood count, which was taken daily, returned to normal in 9 days. During this interval, the sole treatment was omission of the amidopyrin.

After 32 days without medication (Aug. 8) it was again given in daily doses of gr. xx for 14 days (a total of 280 gr.). The neutropenia then reappeared, as shown in Table 1. Other signs and symptoms were also present and the patient complained of malaise, headache, general body aches and a poor appetite, but these appeared 24 hr. after the neutropenia was discov-

ered. The next day there was a sudden attack of nausea, vomiting, hypogastric pain, chills and the temperature rose to 102°. The W. B. C. were 3800 with 2% polys. At this point we were afraid that simply abstaining from the amidopyrin would not be sufficient to eliminate the neutropenia, and pentnucleotid was given intramuscularly and glucose solution intravenously. Within 9 days after the omission of the drug, the blood count was again normal and has remained normal to date. There was no sore throat at any time.

TABLE 1.—BLOOD COUNTS OF CASE 1.

Date.	R. B. C. in millions.	W. B. C. in thousands.	Differential.						
			Polys.	Lymph.	Mono.	Eosino.	Baso.	Myelo.	Promyelo.
5-13-1933	4.25	10.0	68	22	4	6	0	0	0
5-17-	....	12.4	64	28	4	6	0	0	0
6- 6-	5.2	11.5	60	32	6	2	0	0	0
6-16-	5.4	11.8	68	30	2	0	0	0	0
6-26-	5.07	4.0	2	56	8	6	2	26	0
6-27-	....	4.1	3	57	2	11	2	23	2
6-28-	5.15	5.8	12	63	2	6	0	17	0
6-29-A.M.	5.45	6.4	15	47	2	13	1	22	0
6-29-P.M.	5.45	6.3	27	53	1	3	0	16	0
7- 1-	....	7.0	26	47	7	7	1	12	0
7- 3-	4.61	10.8	47	41	3	6	1	2	0
7- 5-	4.80	12.5	60	34	4	0	0	2	0
7- 6-	5.20	11.9	65	27	3	2	0	3	0
7-22-	....	11.0	64	28	6	2	0	0	0
8- 2-	....	10.8	39	33	4	4	0	0	0
8-12-	5.00	11.4	66	24	6	2	2	0	0
8-15-	5.50	10.7	60	30	8	2	0	0	0
8-17-	5.35	10.4	56	36	2	6	0	0	0
8-21-	....	6.3	27	42	2	3	0	26	0
8-22-A.M.	....	4.0	6	45	4	6	0	37	0
8-22-P.M.	....	3.8	2	38	4	6	0	50	0
8-24-A.M.	4.14	5.3	11	39	0	0	0	50	0
8-24-P.M.	....	8.4	26	39	1	3	1	30	0
8-25-A.M.	....	7.8	39	36	1	6	1	17	0
8-25-P.M.	....	7.8	33	35	3	4	0	25	0
8-26-A.M.	....	10.1	48	29	5	6	0	12	0
8-26-P.M.	....	9.0	42	40	0	8	0	10	0
8-29-	....	7.5	62	24	4	0	0	10	0
8-30-	....	11.1	70	18	0	2	0	10	0
8-31-	....	11.4	62	27	0	4	0	0	0
9- 5-	....	9.5	74	23	1	2	0	0	0
9-11-	4.3	10.7	64	27	3	3	0	3	0

CASE 2.—Mrs. R. P., Italian, aged 33, admitted December 3, 1932, complained of swelling and pain in the fingers of both hands and pain in both knees of 2 months' duration. Past history was unimportant except for cholecystectomy in 1927. The blood count on admission was: R. B. C. 3,800,000, W. B. C. 6200, polys. 56, lymph. 44%. The blood Wassermann reaction was negative. On Jan. 7, 1933, 4 tablets each consisting of a combination of magnesium carbonate gr. iv and amidopyrin gr. iiss were given daily. This was continued until Jan. 20 (13 days) when the medication was increased to 5 tablets daily. On Feb. 4 the patient complained of occasional headaches with some nausea but no vomiting. The W. B. C. was 5000 with 30% polys. The medication was discontinued. She had received a total of 275 gr. of amidopyrin in 28 days. The largest daily dose was gr. xiiss. On Feb. 6 the W. B. C. were 3000 with 2% polys. We did not see the patient again but her family physician stated that on Feb. 7, 24 hr. later, she developed an acute sore throat with edema, pyrexia and nausea and vomiting.

On Feb. 10 she was admitted to the Willard Parker Hospital in an extremely prostrated and semicomatose condition. The temperature was 106.8°. A laryngoscopic examination revealed an ulceration of the left

side of the pharynx which extended down to the epiglottic and arytenoid regions—the mucosa appearing black-purple, with many petechiæ. The epiglottis was very edematous and angry red. The posterior arytenoid portion was greatly swollen and red and obscured the glottis. The W. B. C. were 500 with no polys. She was given a transfusion but failed rapidly and died 12 hr. after admission.

Autopsy.* A marked edema, almost a cellulitis of the neck: a marked congestion throughout both lungs; and the heart showed petechial hemorrhages on the left auriculoventricular juncture. The local lesions in the buccal cavity showed a moderate edema and thickening of the base of the tongue and an ulcerated area over the left tonsillar region extending down to the posterior pharyngeal wall to involve the arytenoid fold. The entire epiglottis was moderately edematous but the glottis on the left was so edematous as to extend beyond the midline on the right. The larynx, similarly, showed marked edema of the cords and the tracheal mucosa, likewise, showed moderate edema and congestion.

The *liver* was moderately congested and showed a considerable yellowish discoloration with evidence of fatty degeneration. There was no apparent bile stasis and no cirrhosis.

The *spleen* was purplish-red in color and the capsule was tense. On section, there was obvious acute congestion. The normal architecture was rather obscured and there were no discernible follicles. The medullæ of the *adrenals* were somewhat thicker than the average and rather hemorrhagic in appearance. The *thymus* was persistent but of normal appearance. The *lymph nodes* in the cervical region, around the trachea and at the bifurcation of the primary bronchi, were extremely large, dirty grayish-red in color and on section some showed an acute necrosis with pus formation. *Anatomical diagnoses:* Acute ulcerative arytenoiditis; acute edema of the epiglottis, glottis and larynx; agranulocytosis; persistent thymus.

Microscopic Examination. *Heart.* A marked interstitial edema with moderate congestion, which seemed to be a part of the acute process and an interstitial cellular infiltration, entirely monocytic in character, was present.

Liver. There was moderate congestion of the sinuses, particularly in the central areas, with an almost complete absence of white cells in the sinuses. Many of the nuclei centrally showed marked hyperplasia suggesting the possibility of previous central necrosis with regeneration.

The portal areas showed slight monocytic cell infiltration around the bile ducts.

Spleen. There was extreme congestion and the follicles were prominent and numerous but of average size. There was very little activity in their germinal centers. There was a diffuse reticulo-endothelial hyperplasia with connective tissue increase of the stoma. No granulocytes were noted in the congested pulp.

Adrenals. There was a moderate congestion with more fatty vacuolization than normal in the cortical cells.

Organs of the Neck. Sections from the ulcerative area of the throat and the adjacent tissues presented evidence of an extreme degree of edema. This extended into the musculature widely separating the muscle fibers, many of which showed extensive degeneration. There was a diffuse bacterial invasion of the tissues, mostly streptococcal, but there was a complete absence of cellular infiltration except a few scattered lymphocytes and large mononuclear phagocytes.

Bone Marrow. Sections from the femur showed many clumps of reticulo-endothelial cells and lymphocytes and plasma cells and islands of red-cell

* We are indebted to Dr. Lawrence W. Smith and the authorities of the Willard Parker Hospital, Department of Hospitals, New York City, for the autopsy report.

activity were present. Megakaryocytes were present in moderate numbers and a few early myeloid cells, chiefly undifferentiated, were noted. Essentially, there was no myeloid activity. These changes were similar in the marrow from the vertebral column and ribs but there were more early myeloid cells in the vertebrae.

Discussion. Two instances of neutropenia developing while the patients were receiving amidopyrin are presented. Patient 1, returned to normal 9 days after the drug was omitted, without any other form of treatment. After a period of rest the amidopyrin was resumed. This was followed by neutropenia after the patient had received about the same amount of the drug as on the previous occasion (280 gr.). The W. B. C. returned to normal in 8 days or about the same time as after the first attack. The rapid recovery after the omission of the drug, in one instance without therapy and in the other with only 4 injections of 10 cc. each of pentnucleotid would seem to indicate that the neutropenia was probably produced by the amidopyrin. The second fatal case was the first instance of this phenomenon observed in the clinic and at that time we were uncertain as to whether amidopyrin played a part in its etiology. In the light of our recent experience we feel certain it was caused by the amidopyrin. Although the second patient was taking a combination of magnesium carbonate and amidopyrin, the fact that Patient 1 developed two attacks of neutropenia after the use of amidopyrin alone, we believe, eliminates any probability that magnesium might have played any part in the condition. A predisposition to neutropenia may have existed in these patients or the onset may have been due to the inability of the bone marrow to cope with any additional strain which may have been brought on by the amidopyrin. Neutropenia is frequently periodic in character and may be produced by several factors as pointed out by Beck.[2] Farley[3] reviewed 39 cases appearing in the literature in which the function of the bone marrow was depressed following the use of various preparations of arsphenamin. Taking these into consideration and recognizing that benzene is a powerful leukocytic depressant, it is possible that amidopyrin, a benzene derivative, could be an etiologic factor.

The above 2 cases occurred in a series of 200 patients receiving the drug. In 2 other patients, the poly. counts were reduced from 55 and 60% to 35 and 40% respectively while taking amidopyrin, but the poly. counts promptly returned to normal when the drug was omitted. Two others in the series developed nausea, vomiting, exhaustion, pyrexia, etc., but blood counts were not obtained. It is possible that these cases may have been similar to the 2 cases detailed above and that they may have made spontaneous recovery when the drug was omitted.

Conclusions. 1. Evidence is presented that 2 patients and possibly 4 others developed neutropenia while taking amidopyrin.

2. It is suggested that the adoption of periodic blood counts in patients receiving amidopyrin may prevent the onset of this syndrome.

3. The drug should be temporarily discontinued following symptoms suggestive of intoxication.

I wish to express my thanks to Dr. A. S. Price, pathologist of the hospital, for his coöperation in studying the hematology of these cases.

NOTE.—Since this paper was submitted the following articles have appeared: Watkins, C. H. (The Possible Rôle of Barbiturate and Amidopyrin in the Causation of Leukopenic States, *Proc. Staff Mayo Clinic*, **8**, 713, 1933), reported 32 cases of granulocytopenia. Amidopyrin was responsible for 10 cases, 2 of which were fatal. Two cases were considered due to amidopyrin plus diallyl barbituric acid, but no deaths occurred. Five fatal cases were attributed to isoamyl-ethyl-barbituric acid. F. W. Madison and T. L. Squier (The Etiology of Primary Granulocytopenia [Agranulocytic Angina], *J. Am. Med. Assn.*, **102**, 755, 1934) studied 14 patients, each of whom had taken drugs containing amidopyrin either alone or in combination with a barbiturate. Except in the severe cases, the patients recovered when the drug was discontinued. An additional case with fatal termination has been brought to my attention through the courtesy of Dr. C. W. Lieb (personal communication). M. C., aged 78, had osteoarthritis of 6 months' duration. She had been taking 5 gr. of amidopyrin daily for 2 months. The blood count at that time was normal. The following month she had taken 10 gr. of amidopyrin daily. After the third week of this medication she came under Dr. Lieb's care. The blood count was: white blood cells 240, with no neutrophils and 10% monocytes. Highly toxic strains of S. aureus were isolated from postnasal cultures and toxic streptococci were recovered from the throat. She was given 3 transfusions, pentnucleotid and liver extract without effect on the blood count.

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A NOMOGRAPH FOR SIMPLIFYING COMPUTATION OF THE URINE SEDIMENT COUNT (ADDIS).*

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IT is the experience of many that the most difficult part of the urine sediment count of Addis[1] is the computation of the results rather than the making of the count itself. In an effort to lessen this labor the accompanying nomograph was devised.

In the sediment count computation is required for the determination of five quantities: (1) the 12-hour volume of urine; (2) the total protein excretion; (3) the cast count; (4) the red cell count, and (5) the white and epithelial cell count. The raw data on which these computations are based include: (1) the period of time over which the urine is collected; (2) the volume of the voided urine; (3) the volume in which the sediment is mixed; (4) the numbers of

* Supported, in part, by a grant from the Rockefeller Fluid Research Fund of the School of Medicine, Stanford University.

each of the formed elements counted per unit volume of counting chamber, and (5) the volume of protein precipitate.

The nomograph consists of scales representing the above variables, constructed in such a way that any straight line intersects related scales at corresponding points. For example, the 12-hour urine volume depends on the volume of urine voided and the period over which it is collected. If a convenient form of straight line such as a taut thread be placed across Scales A and B intersecting them at points corresponding to the last two variables above, the straight line will be found to intersect Scale C at a point giving the 12-hour volume. This procedure is repeated, combining various scales to compute various data.

The scales of the nomograph are logarithmic and consequently non-uniform. They are used in alphabetical order, A and B being combined to give a reading on C, C and D together giving a reading on E, and E and F giving values on G. A time-saving exception to this order is to compute the protein excretion (by means of Scales C, J and K) immediately after C is determined and before going on to D and E. With reasonably careful setting and reading of the values on the nomographic chart of size 8½ by 11 inches,* the mathematical error will be less than 5 per cent, a departure which is well within the limit of the method.

The scales for calculation of the protein excretion apply to Dr. Addis' modification of the technique of Shevky and Stafford,[2] from which it differs only in the use of graduated centrifuge tubes of 6.5-cc. instead of 13-cc. capacity. With the 13-cc. tube the result obtained from the nomograph is divided by 2.

The counts are made in the ordinary blood counting chamber, each of the two sections of which has a ruled area 3 mm. square. The 9 primary 1-mm. squares thus formed are easily identified because adjacent ones are differently subdivided. For the purpose

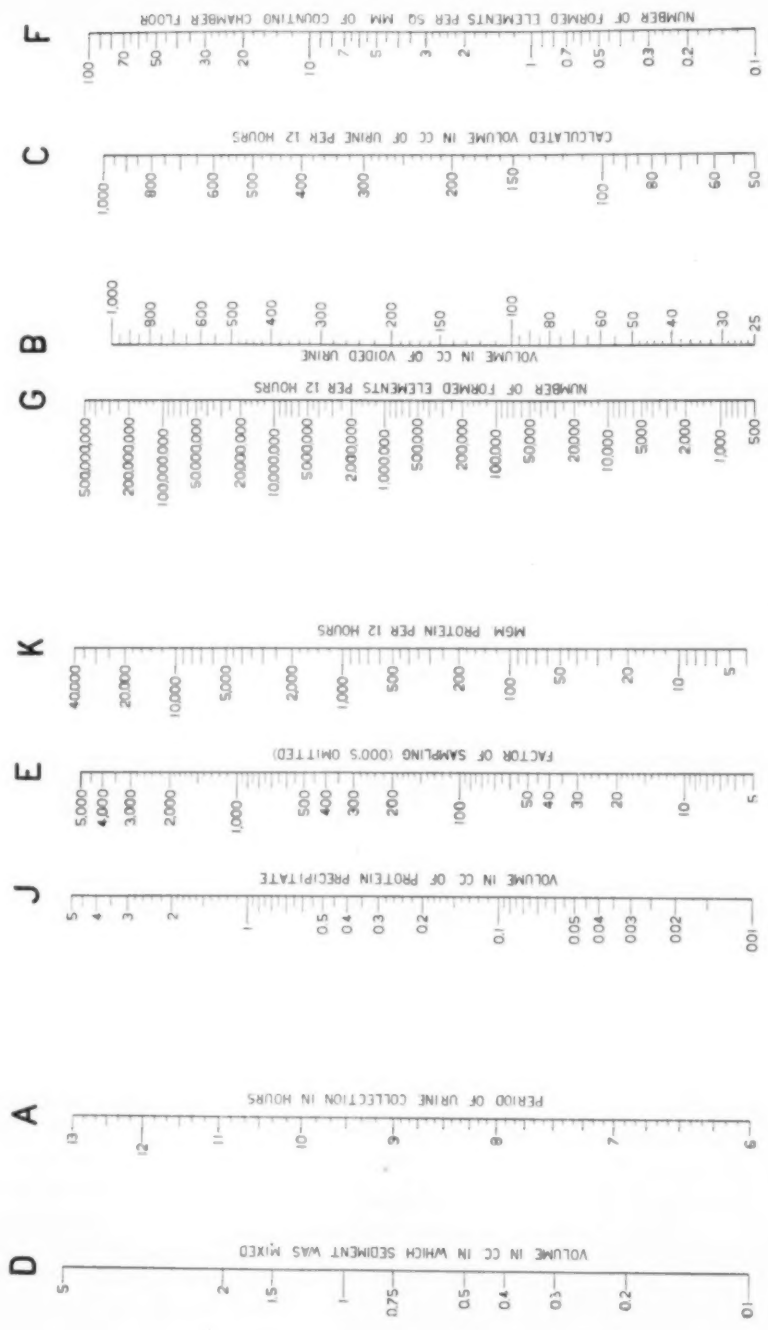
NOMOGRAPH FOR THE COUNT OF URINE SEDIMENT (ADDIS).

To use the nomograph place a straightedge across the two designated scales, intersecting them at given values and read at the intersection with a third scale a derived value. The scales A, B, D, F and J include the original data obtained in the study of the urine. The scales C, E, G and K give derived data. To calculate the count of the urine sediment:

1. Using scales A and B, obtain a value on scale C.
2. Using the newly found point on scale C in connection with scale J, read from scale K. (Scale K applies to Dr. Addis' modified technique for protein, using a 6.5-cc. graduate centrifuge tube. For the original technique using a 13-ml. tube, divide the obtained value by 2.)
3. Using scales C and D, read from scale E.
4. Connecting the obtained point on scale E with successive points on scale F, read from scale G the values for the respective formed elements.

Formulæ for checking: $C = \frac{12\,B}{A}$. $G = 1000\,CDF$. $K = 7.2\,CJ$.

* Nomographic charts 8½ by 11 inches in size may be obtained from J. W. Stacey, Inc., Flood Building, San Francisco, Calif., at a cost of twenty-five cents each.


F
NUMBER OF FORMED ELEMENTS PER SQ. MM. OF COUNTING CHAMBER FLOOR
100 70 50 30 20 10 7 5 3 2 1 0.7 0.5 0.3 0.2 0.1
C
CALCULATED VOLUME IN CC OF URINE PER 12 HOURS
1,000 800 600 500 400 300 200 150 100 80 60 50
B
1,000 800 600 500 400 300 200 150 100 80 60 50 40 30 25
VOLUME IN CC OF VOIDED URINE
G
NUMBER OF FORMED ELEMENTS PER 12 HOURS
500,000,000 200,000,000 100,000,000 50,000,000 20,000,000 10,000,000 5,000,000 2,000,000 1,000,000 500,000 200,000 100,000 50,000 20,000 10,000 5,000 2,000 1,000 500
K
MGM PROTEIN PER 12 HOURS
40,000 20,000 10,000 5,000 2,000 1,000 500 200 100 50 20 10 5
E
FACTOR OF SAMPLING (000'S OMITTED)
5,000 4,000 3,000 2,000 1,000 500 400 300 200 100 50 40 30 20 10 5
J
VOLUME IN CC OF PROTEIN PRECIPITATE
5 4 3 2 1 0.5 0.4 0.3 0.2 0.1 0.05 0.04 0.03 0.02 0.01
A
PERIOD OF URINE COLLECTION IN HOURS
13 12 11 10 9 8 7 6
D
VOLUME IN CC IN WHICH SEDIMENT WAS MIXED
5 2 1.5 1 0.75 0.5 0.4 0.3 0.2 0.1

of computation with the nomograph, the 1-mm. square is taken as unit area in terms of which the elements are enumerated.

As with all procedures in which a distribution within a large quantity is estimated by enumeration in small samples, the count of the formed elements of the urine is subject to an unavoidable error due to chance variations of distribution in the samples counted. Such an error may be considerable, and it is of value to know its size.

One index to the magnitude of the error of sampling in the sediment count of the urine may be obtained from Scale E, which gives the number of thousands of formed elements per 12 hours represented by 1 element per sq. mm. of counting chamber floor. For example, if the point obtained on Scale E should be 40, each cast or cell in an average sq. mm. of counting chamber floor would represent 40,000 in the 12-hour urine, an error of 1 cast or cell per sq. mm. would cause an error of 40,000 in the total count, an error of 10 per sq. mm. would make a difference of 400,000 in the total, and so forth.

The factor of size of sample demands particular consideration in the cast count, where the upper limit of normal is only 5000 to 10,000. Here, for instance, with a reading of 40 on Scale E, it would be meaningless to glance over 1 sq. mm., find 1 cast, and conclude that there were 40,000 casts in the 12-hour excretion. Enough squares must be counted so that an error of a few elements in the number counted makes a difference which falls well within the limit of normal. It is consequently suggested that the "factor of sampling," as Scale E has been labeled, be calculated before the actual count is made, so that one can have in mind the significance of a single cell or cast.

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PNEUMOCOCCUS ANTIBODY SOLUTION IN THE TREATMENT OF LOBAR PNEUMONIA.

RESULTS IN 130 CASES.

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The specific treatment of the pneumococcic pneumonias has received considerable attention in recent years. For a time interest was centered more or less on Pneumococcus Antibody Solution

(Huntoon's Antibodies), but more recently attention has been confined to the use of serum almost to the exclusion of the other product. We believe that this is, to some extent, unfortunate. The antibody solution has been shown in the careful studies of Conner[1] to reduce the mortality in all types of pneumococcic pneumonia from 30 to 11 per cent approximately, and in the studies of Cecil and Larsen[2] from 28 to 21 per cent. In Type I cases the reduction was from 22 to 13 per cent, and in Type II from 40 to 28 per cent.[2] In cases of Type I pneumonia treated within 48 hours of onset, deaths decreased from 23 to 9 per cent.[3] This compares favorably with results obtained with Felton's serum in Type I and Type II cases. Conner's work shows antibody solution to be of value in Type III and Group IV pneumonias, in which serum is ineffective, while Cecil's does not.

Although antibody solution is occasionally productive of chills and a rise in temperature when injected intravenously, we did not encounter the numerous and severe reactions described by Conner and Cecil, and believe this preparation decidedly less objectionable than serum on this score. We are informed that the pyrogenic property of the earlier preparation of antibody solution, which was used by Cecil and Conner, was largely eliminated by a change in the distilled water used in its manufacture, and our experience bears this out.

This study comprises 130 treated and 52 untreated cases observed from 1927 to 1931 inclusive. No effort was made to form a control group, but the untreated cases serve roughly as controls. These represent, for the most part, cases in the care of physicians who were not interested in Pneumococcus Antibody Solution. These patients received no other specific treatment. Oxygen was used in a few, and a few were given blood transfusions, but for the most part their treatment consisted of careful nursing and dieting, with administration of circulatory stimulants when necessary. The solution was not reserved for selected or favorable cases, but rather the contrary, so that the treatment group includes a fair proportion of "bad risks." Treatment was given, if at all, without regard to age of patient, complications, or day of illness. Although every effort was made to have complete bacteriological studies on every case, and to give treatment early and adequately, a considerable proportion of cases escaped some part of the routine. We believe, however, that this performance is as good as can be obtained in an open hospital and in private practice, and perhaps has an added value as demonstrating what results may be expected under these, that is, under ordinary conditions.

Typing was done by the Avery method, the results from the peritoneal exudate of the mice being checked by heart blood cultures. In addition, direct plates of sputa were made in order to detect more surely the non-pneumococcic cases.

Treatment. Specific treatment was started as soon as the clinical diagnosis was made, and before the completion of bacteriologic studies, because of the well recognized importance of beginning injections of either antibodies or serum as early in the disease as possible. If the infection proved not pneumococcic, treatment was discontinued. Although expensive, this step saved valuable time in many cases. In more than half the cases early diagnosis was greatly aided by the Roentgen ray, and we are indebted to Dr. George U. Pillmore for his coöperation in this feature. The dose of antibody solution was usually 50 cc. intravenously 3 to 4 times a day in adults and 25 cc. in children. When the intravenous route was not feasible, intramuscular injections up to 50 cc. per dose were used. After a little experience with the solution, fear of reactions was lost and doses were enlarged in some instances to 100 cc. t. i. d. in adults and 50 cc. in children. The average total amount of antibody solution used was 460 cc. for the perfectly controlled group and 343 cc. for the imperfectly controlled group of adults, and 193 cc. for children. The largest amounts given were 1200 cc. intravenously to a man aged 37 years over a period of 13 days, and 650 cc. intramuscularly to a child aged 1 year over a period of 7 days. In neither was there any reaction and both recovered.

TABLE 1.—RESULTS OBTAINED WITH PNEUMOCOCCUS ANTIBODY SOLUTION IN LOBAR PNEUMONIA IN SUBJECTS 12 YEARS AND OVER.

	Lived	B.C.	Died	B.C.	Mortality, per cent.	Average days ill.
Perfectly Controlled:						
Type I	3	0	2	1	40	
Type II	3	1	3	1	50	
Type III	8	4	1	0	11	
Group IV	18	1	2	1	10	
	32	6	8	3	20	24.2
Imperfectly Controlled:						
Type I	2	0	4	4	66	
Type II	1	0	1	1	50	
Type III	5	0	3	0	37	
Group IV	9	0	3	2	25	
Untyped	11	0	0	0	0	
	28	0	11	7	28	25.3
Untreated:						
Type I	4	0	3	2	43	
Type II	4	0	0	0	0	
Type III	2	0	3	2	60	
Group IV	4	0	2	2	33	
Untyped	7	0	4	0	36	
	21	0	12	6	36	25.6

Perfectly controlled: Treatment begun within 72 hours of onset, adequate dosage.
Imperfectly controlled: Treatment started late, inadequate dosage, etc.
B.C.—Blood culture positive.
Average days ill: The duration of the disease from onset to discharge from hospital of uncomplicated recovered cases only.

A distinct impression was obtained that the larger doses were more effective, especially in producing early crises. The large doses too, were possibly more economical than the small, as the total of solution used was less when the illness was quickly terminated. Treatment was continued for 24 hours after the temperature first reached normal, either in full, or in half doses, as in several of the early cases the temperature again rose to its former height when injections were discontinued immediately after the crisis, or lysis.

TABLE 2.—RESULTS OBTAINED WITH PNEUMOCOCCUS ANTIBODY SOLUTION IN LOBAR PNEUMONIA IN SUBJECTS UNDER 12 YEARS.

	Lived.	Died.	Mortality, per cent.	Average days ill.
Treated	48	3	6	19.8
Untreated	12	7	37	24.1

Very few children studied bacteriologically. Antibodies given mostly intramuscularly.

Comment. It is realized that the numbers included in each group are too small to be of great statistical value. However, the total mortality for the various groups seems significant. Thus the mortality of untreated adults is nearly twice that of the adequately treated group, the imperfectly treated group falling between. Of more significance are the results in those cases with positive blood cultures. Of 13 cases with positive blood cultures in the untreated and the inadequately treated groups all died, while of 9 such cases in the well treated group 6 recovered. An observation not to be reduced to statistics, but very impressive to the clinician, was the rapid conversion of not a few highly toxic cases with rapid pulse, cyanosis and delirium to a much more favorable state, even though an early crisis did not result. One gained the impression that the solution was life saving in such instances.

The average duration of the infection in the treated and untreated cases differed little in the adults, although more materially in children. It might be inferred that the effect of the antibody solution was to combat the more severe toxic manifestations of pneumonia and possibly to sterilize the blood stream, thus reducing mortality, without shortening the course of the infection.

Antibodies appeared to have a distinctly favorable effect in Type III and Group IV cases in our series, which is in accord with the reports of Conner and of Huntoon.[5] This is an observation of definite importance. In the group of children the mortality of the untreated is much greater than the average for lobar pneumonia, and this gives an exaggerated importance to the effect of antibody solution. On the other hand, we feel that the solution was of considerable benefit in this group. Of importance is the fact that such results as were obtained were secured by means of intramuscular administration for the most part. In this connection the results of Cecil and Baldwin[4] with subcutaneous injections are of interest. These, although inferior to those following the intravenous route, were worth while, the mortality reduction being from 39 to 24 per

cent in cases treated within 48 hours of onset of the infection. It might reasonably be supposed that intramuscular administration would be more effective than subcutaneous, and it is our belief that antibody solution given into the muscles of children, when intravenous administration is not feasible, is not only distinctly worth while, but greatly enlarges the field of usefulness of the method.

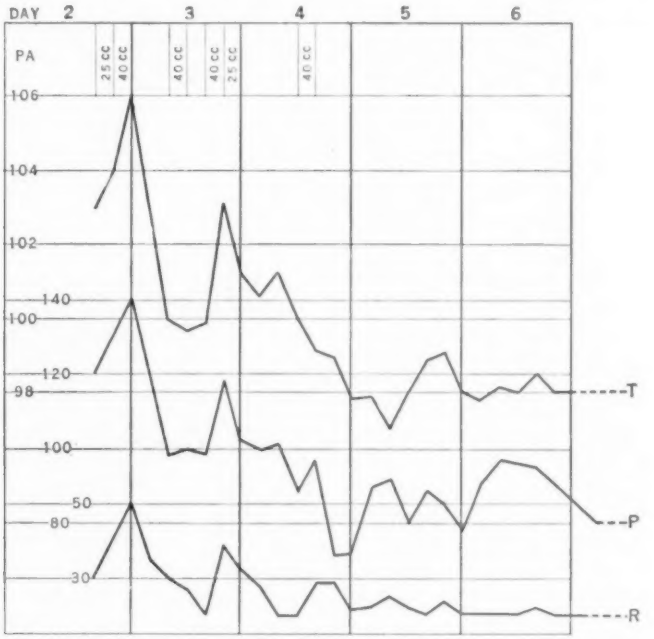

CHART 1.—T. C., age 9 years. Intravenous injections of pneumococcus antibody solution continued in spite of an initial rise of temperature. Early crisis.

We feel that cases of lobar pneumonia, which for one reason or another cannot be diagnosed bacteriologically, should, nevertheless be treated specifically, as the great majority of such pneumonias are due to pneumococci, 83 per cent according to Cecil and Larsen. For this purpose Pneumococcus Antibody Solution is logically the method of choice, since it is effective against Types I, II and III, and Group IV pneumococci, while the use of serum is confined to Types I and II. On the other hand, we by no means advocate the indiscriminate use of antibodies. Whenever at all possible the bacteriology of sputum and blood should be determined, and the remedy discontinued in non-pneumococcic cases, in which the injections are useless, expensive, and harmfully annoying to the patient.

Complications. Empyema occurred once in the well managed cases, 4 times in all others. Delayed resolution was observed twice in those inadequately treated. Otitis media and mastoiditis accompanied the pneumonia in several of the children.

Reactions. A fear of dangerous reactions has remained fixed in the mind of many physicians after the experiences of Conner and of Cecil with Pneumococcus Antibody Solution as originally manufactured. In our series of cases harmful reactions did not once occur. In 2 adults a chill with a rise of fever to 106° occurred after the administration of 100 cc. of solution intravenously, and in 1 adult after a dose of 50 cc. In a 4th adult a mild but similar reaction followed a dose of 90 cc. A dose of 25 cc. in a child aged 10 years caused a similar chill and rise of fever to 106. The pulse and respiration were not much affected, nor were there any other manifestations. The reactions come on from 2 to 4 hours after the injections. In each case the reaction was followed promptly by a pseudocrisis with improvement in the general condition of the subject. Other manifestations were recorded as reactions, such as increase in rate of respiration, nausea, pain in the back, but careful review of the records make it questionable whether these can be attributed to the solution. Thus, an incidence of five definite reactions, none harmful, in several hundred injections, does not furnish reason to fear this result. In all these cases similar doses were given either before or after the reactions without any untoward effect. No systemic reactions followed intramuscular administration, and local reactions were remarkably mild even when large quantities were injected.

Pneumococcus Antibody Solution was made available for ward patients of Bryn Mawr Hospital through the generosity of the late Mr. Samuel Rea and other members of the Board of Trustees, the late Mrs. Samuel G. Dixon and others of the Women's Board of Managers, and others.

Summary. Pneumococcus Antibody Solution was observed to effect a definite reduction in mortality in 130 cases of lobar pneumonia of all types and ages as compared with 52 cases not specifically treated.

It appeared to be of distinct value in Type III and Group IV cases, as well as in Types I and II.

It appeared to be of value when given intramuscularly in infants and children.

Its effect was most marked in cases treated within 72 hours of the onset of the infection, and with large doses.

It is rarely productive of reactions.

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BOOK REVIEWS AND NOTICES.

LABORATORY MEDICINE. By DANIEL NICHOLSON, M.D., Member of the Royal College of Physicians, London; Assistant Professor of Pathology, University of Manitoba, etc. Pp. 566; 124 illustrations, 3 colored plates. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, $6.50.

THIS is a compact but comprehensive work dealing with the modern phases of laboratory medicine—amply illustrated and written in simple, easily followed style. The chief advantage of this book over other modern works lies in the author's unique method of organization and presentation of the large amount of material, both old and new, that has accumulated in clinical pathology. The selection of methods is based primarily on simplicity, with simple directions in technical details and lucid interpretations. For both students and technicians the sources of error, with simple reasons, follow each procedure. The general practitioner will find the common routine procedures briefly and conspicuously outlined. These are procedures that can be done in office and bedside practice and because of their simplicity they enable the practitioner to use and enjoy the rapidly expanding knowledge in laboratory medicine. A few of these procedures are modern skin tests with illustrated reactions, prophylactic laboratory treatment of measles, whooping cough, etc., accompanied by suitable simple laboratory tests. The colored plate illustrating Benedict's urinary sugar reactions, to the Reviewer, is unique and satisfying.

For everyone's use the indications for expensive tests and rare or unusual examinations are given, which, if followed, will prevent considerable duplication of results with saving of time and expense. The procedures are first given in brief in heavy type, followed in detail in ordinary legend form. This thoughtfulness on the part of the author will prove a time saving to many. An inspection of the book should convince one of its value.

J. B.

FORMES, VIE ET PENSÉE. By J. BEAUVERIE and others. Pp. 419; illustrated. Lyon: Librairie Lavandier, n.d. Price, 20 fr.

THIS, the fourth of the series published by the Lyons group on philosophic and biologic aspects of medicine, deals with structural relation between crystalline and organic forms, elementary and embryonic structures, the relation of structure to adaptation, endocrine influences and a final synthesizing chapter on form and function. It supplements the preceding volume on "Les Rhythmes de la Vie" (reviewed AM. J. MED. SCI., **186**, 581, 1933). The same method has been followed, as previously, of having a different member of the group write each chapter—thus providing a breadth of points of view even if at the cost of some overlapping and differences of opinion. The Abbe Monchanin, who, as in the past, contributes the final chapter, invokes the rhythms of life and mind as incitants to a return toward God and his works. Though little or no proof is attempted or possible, the book will prove stimulating along little traveled lines of thought.

E. K.

HUMAN SEX ANATOMY. By ROBERT LATOU DICKINSON, M.D., F.A.C.S. Pp. 145; more than 1000 illustrations. Baltimore: The Williams & Wilkins Company, 1933. Price, $10.00.

THE previous publications of the National Committee on Maternal Health have covered various aspects of sex and the sex relation. As a

definite program developed, the need for an atlas, a basic portrayal of the normal anatomy of the two sexes and of the anatomy of coitus and contraception became apparent. To meet this demand Dr. Dickinson has edited the present volume on Human Sex Anatomy.

The book is divided into two parts, the first section (132 pages) correlates the atlas proper with a description of the plates, their source and the scales upon which they were drawn, with a running commentary upon the normal and abnormal anatomy of the genital organs, as well as the anatomical and functional relations exercised in coitus. Frank as the discussion and illustrations are, one is not a little surprised to find that one plate, not included in the atlas, is to be sent to medical purchasers of the book only at their personal request.

The atlas comprises 172 figures, but there are over a thousand separate drawings on these plates. Dr. Dickinson's pencil has been as able as his pen was fluent and the many original drawings reflect not only his ability as an artist of consummate skill but his thorough understanding, as a physician, of the point he wished to illustrate.

The anatomy of the female reproductive organs in diagram, line sketch and half tone from hundreds of sources show every possible view by dissection and sagittal and oblique section, illustrating the part these organs play in the sex act. The anatomy of the male genital structures is portrayed in an equally exhaustive manner. The anatomy of coitus represents an entirely new approach to an understanding of the anatomical relations involved in this dual function in the different positions portrayed. The anatomy of contraception illustrates many methods of contraception and many devices which are used.

This book certainly fulfills the need as stated. To those whose advice is sought regarding sex, sexual or marital problems, the text will offer much. Many problems in sex research are suggested. P. W.

Cold Spring Harbor Symposia on Quantitative Biology. Volume 1. Pp. 239; illustrated. Cold Spring Harbor, L. I., N. Y.: The Biological Laboratory, 1933. Price, $2.90.

In furtherance of this Laboratory's purpose of developing the field of quantitative biology through the coöperative effort of biologists, chemists, physicists and mathematicians, a distinguished group was invited there last summer to carry on their investigations, and during one month to give lectures and take part in symposia. This monograph, presenting 28 topics, extending over a wide range, represents the first fruits of an interesting and important experiment in the acquisition and diffusion of scientific knowledge. The method has already so demonstrated its value that fortunately we may expect a series of volumes which will make available these "last words" to a wide circle. For they represent a galaxy of stars that it would be hard indeed to surpass. Lectures (revised and grouped for publication) by Hans Müller and Abramson on electrophoresis, the diffuse double layer, the stability of colloids, and so on, unite with studies on conductance by Cole, on agglutination and phagocytosis by Mudd, on the biophysics of respiratory proteins by Svedberg. Neurophysiology is represented by Cole, Gasser and A. V. Hill, osmosis by Briggs, Osterhout and Ponder, oxidation-reduction by Barnett Cohen, Chambers and Michaelis. Only one article on pH appears (by D. A. MacInnes), while some aspects of the physical chemistry of the blood are presented by van Slyke, and the electric impedance of cell suspensions is given by Hugo Fricke, the first director of the biophysical laboratory (1928). Short discussions of various lectures add to the background. If this initial high standard is maintained, it is difficult to see how a worker in this field can do without these volumes or fail to attend future symposia at Cold Spring Harbor. E. K.

NEW BOOKS.

External Diseases of the Eye. By DONALD T. ATKINSON, M.D., Consulting Ophthalmologist to the Santa Rosa Infirmary and the Nix Hospital, San Antonio, Texas, etc. Pp. 704; 479 illustrations. Philadelphia: Lea & Febiger, 1934. Price, $7.50.

Chinese Medicine. By WILLIAM B. MORSE, M.D., LL.D., F.A.C.S. Vol. XI of Clio Medica series. Pp. 185; 20 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, $2.50.

The Medical Clinics of North America, Vol. 17, No. 5 (New York Number—March, 1934). Pp. 324; 32 illustrations. Philadelphia: W. B. Saunders Company, 1934.

Medicine. A Voyage of Discovery. By JOSEF LÖBEL, M.D. Translated from the German by L. MARIE SIEVEKING and IAN F. D. MORROW. Pp. 334. New York: Farrar & Rinehart, Inc., 1934. Price, $3.00.

The Cyclopedia of Medicine, Volume 8. GEORGE MORRIS PIERSOL, B.S., M.D., Editor-in-Chief, and EDWARD L. BORTZ, A.B., M.D., Assistant Editor. Chief Associated Editors: W. WAYNE BABCOCK, A.M., M.D., CONRAD BERENS, M.D., P. BROOKE BLAND, M.D., FRANCIS L. LEDERER, B.S., M.D., A. GRAEME MITCHELL, M.D. Pp. 1083; illustrated with half-tone and line engravings, also full-page color plates. Philadelphia: F. A. Davis Company, 1933.

Japanese Medicine. By Y. FUJIKAWA, M.D. Translated by JOHN RUHRÄH, M.D., Vol. XII of Clio Medica series. Pp. 114; 8 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, $1.50.

Brucella Infections in Animals and Man. By I. FOREST HUDDLESON, Department of Bacteriology and Hygiene, Michigan State College. Introduction by WARD GILTNER, Dean, Division of Veterinary Medicine, Michigan State College. Pp. 108; 24 illustrations, 2 in colors. New York: The Commonwealth Fund, 1934. (Price not given.)

A Short History of Some Common Diseases. By DIVERS AUTHORS. Edited by W. R. BETT, M.R.C.S. (ENG.), L.R.C.P. (LOND.), late Resident Medical Officer, Princess Elizabeth of York Hospital for Children, Shadwell, Eng., etc. Pp. 211. London: Oxford University Press, 1934. (Price not given.)

Coccidia and Coccidiosis of Domesticated, Game and Laboratory Animals and of Man. Monograph No. 2, Division of Industrial Science, Iowa State College. By ELERY R. BECKER, D.Sc., Associate Professor of Protozoology, Iowa State College. Pp. 147; 25 illustrations. Ames, Iowa: Collegiate Press, Inc., 1934. Price, $2.50.

The Surgical Clinics of North America, Volume 14, No. 2 (New York Number—April, 1934). Pp. 293; 71 illustrations. Philadelphia: W. B. Saunders Company, 1934.

Acute Intestinal Obstruction. By MONROE A. MCIVER, M.D., Surgeon-in Chief, Mary Imogene Bassett Hospital, Cooperstown, N. Y. Pp. 430; 62 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, $7.50.

NEW EDITIONS.

Essentials of Medical Electricity. By ELKIN P. CUMBERBATCH, M.A., B.M. (OXON.), D.M.R.E. (CAMB.), M.R.C.P., Medical Officer in Charge, Electrical Department, and Lecturer on Medical Electricity, St. Bartholomew's Hospital, etc. Pp. 508; 132 illustrations and 15 plates. Seventh edition, revised and enlarged. London: Henry Kimpton, 1933. Price, 10/6.

PROGRESS
OF
MEDICAL SCIENCE

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF
FRANKLIN G. EBAUGH, M.D.,
PROFESSOR OF PSYCHIATRY IN THE UNIVERSITY OF COLORADO,
AND
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THE PRACTICAL SIGNIFICANCE OF PSYCHOTHERAPY IN GENERAL PRACTICE.

We pride ourselves on the scientific progress of medicine but all the while we may be blinding true sight by a gaudy delusion. Instruments of precision have enhanced our diagnostic ability; microscope and test tube have reduced symptoms to perceptible causes and effects. We jostle molecules and bacteria about as we might trained fleas, we reduce complaints to pathologic changes, and our findings make for us a "case," the clinical course and ultimate results of which we are fairly well able to predict.

The "day of specilization" has removed us still farther from our patient as he would have us see him, and some of us confine ourselves with concern over the gastro-intestinal tract while others of us are content with meting out organotherapy. Truly, a "large scale industry arises, in the running of which there is never a moment's leisure for personal contact between physician and patient and wherein there is no longer a trace of magnetic rapport between the soul of the healer and the soul of the healed."[1]

Because we have been too engrossed in organs and systems, because we have failed to consider the patient in his entirety, his setting in life, his biologic peculiarities, we have missed much to be interpreted as pathologic change not measurable by laboratory methods and have driven our patients to cults and sects for the understanding that we denied them.

Only recently the director of a large outpatient dispensary said:[2] "Today I saw a man who complained of vague surging sensations here and there throughout his body. He remarked that upon dropping his arms to a dependent position at his side all these feelings disappeared. I asked him how many doctors had seen him and he rather boastfully replied 'Oh, I should say between thirty and forty.' Now this man had a blood pressure that, while not strikingly abnormal, warrants

investigating, but outside of this I could find nothing. Either he has something most unusual which all of these men have missed or he is psychoneurotic and it is our job to find out why and do something about it."

How common an example this is of that great cross-section of material seen in our dispensaries, in our offices and upon the wards of our institutions. How readily and willingly we label such a patient "psychoneurotic" and then limit our treatment to telling him it is "just a case of nerves" and send him on his way.

It is useful to recognize three types of these disorders into which the majority of such problems will fall. These are:[3] (*a*) Conversion hysteria, (*b*) anxiety states and (*c*) obsessive states.

Hysteria. Hysteria is the great mimic of somatic disease, particularly simulating any number of neurologic disturbances. To understand the motivation of the symptom we must scrutinize the forces leading to its production by a thorough genetic-dynamic study (*i. e.*, a chronologic study of important life factors dating from birth). With early recognition, an hysterical phenomenon may be checked at its beginning by common sense treatment, or with lack of understanding it may be encouraged in its fixation by making a diagnosis of physical disease.

Though this is not the place for a didactic discussion of hysteria, it would be well to point out the more common forms in which it finds expression.[4] Among them are:

1. Hysterical convulsions closely simulating the *grand mal* attacks.

2. Somatic changes on an hysterical basis, as: (*a*) Anesthesia to touch, pain, temperature and proprioception; (*b*) hyperesthesias; (*c*) paresthesias.

3. Another large group presents motor involvement, such as: (*a*) Hysterical paralyses—monoplegias, paraplegias, hemiplegias; (*b*) contractures—torticollis; (*c*) abnormal movements—astasia, abasia, chorea, trembling movements; (*d*) loss of voice; (*e*) hysterical aphasias; (*f*) benign respiratory ties, as sneezing, hiccoughing, dyspneas; (*g*) spasms—esophageal globus, vomiting, vaginismus, etc.

4. Sensorial changes do not escape; we frequently encounter olfactory and gustatory perversions, loss of hearing, vertigo and visual alterations ranging from restriction of the visual fields and hemianopia to blepharospasm.

Anxiety States. One of the most interesting and common symptom pictures of "nerves" is that seen in attacks of dyspnea, palpitation, sweating, vertigo, precordial discomfort and often gastro-intestinal manifestations with the predominating emotional accompaniment of apprehension, a vague fear of impending danger. Earlier writers attributed these states to frustrated sex excitement or unfulfilled erotic activities. However, with the growing appreciation of a genetic-dynamic study of a problem, we have come to see the anxiety attack resulting not from misdirected sexual activity alone but from any number of daily stresses and strains.

These were the cases so frequently misdiagnosed as hyperthyroidism; these were the cases we called "post flu hearts" in 1918 and 1919 because of the seeming cardiac disorder. An important psychiatric dispensary in this country registered only 80 cases of anxiety states

in the year 1926 when this country was without economic stress, but in the year 1932, when we began to feel the pressure of the depression, 232 such cases were listed.[5]

As anxiety states one may encounter: 1. General irritability—a response to overexcitation, usually with marked tension, pathologic alertness and hyperactivity of auditory sense, particularly.

2. Anxiety attacks in which the outstanding feature is fear—fear of death, fear of a stroke, fear of insanity—together with which there is a disturbance of one of the levels of physiologic functioning, as:

(*a*) Cardiac with palpitation, precordial distress, tightness, fainting, smothering, sinking spells, pain around the heart and substernal pressure.

(*b*) Respiratory—dyspnea, shortness of breath, pain in the chest, tightness in the throat.

(*c*) Gastro-intestinal—diarrhea, constipation, nausea, vomiting, and belching; with the possibility of others, as (*d*) frequency in micturition, vertigo, giddiness, tremor and trembling, night terrors and paresthesias. Of such common occurrence are these and strikingly like organic conditions that they have frequently been diagnosed "angina pectoris, pseudoangina, heart murmur, soldier's heart, effort syndrome, spastic colon, appendicitis, cecal stasis, gastropathy and gastric ulcer."

Obsessional States. This third and last group, though interesting, is less frequently encountered, and because of the involved psychopathologic factors of this group treatment of these patients should not be undertaken by the general practitioner.

It is diagnostic of an obsession that the patient knows its unreality and feels it is derived from something apart from his self. He is conscious of the absurdity involved in his thinking and may attempt to resist its recurrence.

The disorders of obsessive character are doubts, fear states, thoughts and acts.

We are all familiar with the doubt of having turned off the gas heater after retiring, of having put the right letter in the right envelope after posting them. This individual will say to himself, "I *know* I've done it but I *feel* that I haven't."

Similarly, these peculiarities can be analyzed and explanation may be found in the influence of unconscious processes.

General Considerations. A survey of the literature in the past year reveals conclusively the awakening of medical consciousness to the importance of these disorders in general practice. Gillespie's article,[6] perhaps, is outstanding because of its forcefullness in stating the case. In Guy's Hospital about three-fourths of the registered cases were psychoneuroses not resident at the hospital, while but one-fourth comprised the group of institutionalized psychoses. Pervading all practice from gynecology to dermatology are these cases, which masquerade as clinical entities.

There is the current impression that psychotherapy is a specialist's job and necessitates special equipment. However, most of these illnesses require no special technique and can be handled by a common sense approach. The requisites for efficient psychotherapy are a "profound knowledge of human nature," a "good knowledge of general medicine" and ability to spend sufficient time on each individual.

One cannot overemphasize the importance of a good history and clinical observation. Should the physician ask himself what knowledge of psychology he need possess, the answer will be "a knowledge of how psychologic factors can cause what looks like disease."

A most necessary part of the examination is the physical part. It assists in establishing rapport and confidence in addition to having the patient feel that due credit is being given every possibility. Should a "lesion" be found it must be considered in terms of the complaints.

Psychologic examinations are of two types: A "cross-section" examination, in which the complaints are focussed upon and the present status of the patient determined; and a longitudinal study considering the history of the patient himself as well as his illness. The former makes for diagnosis, while the latter is a most useful guide in treatment.

If, in getting the history, the physician focusses attention on the time of origin of the symptoms he will uncover the factors which have produced them. Most common of these are financial concern, domestic affairs, marital difficulties, promotion, demotion, etc.

Best results in the treatment of hysteria are obtained by persuasion. In this manner a "paralyzed" member may be restored and yet the change has been objective enough to impress the patient and, by establishing steadfast *rapport*, make further treatment possible. This method, however, cures only the symptom; but, after all, in many hysterics "cure of the symptom is nearly all that is required."

It may be seen by this survey that no special apparatus is required to produce results but perseverance, accurate investigation and willingness to spend a reasonable time soon after the patient first presents himself.

Obstacles to psychotherapy are pointed out by L. B. Hill,[7] who believes that the cause of the dissatisfaction with current psychotherapeutic activities is to be found in the absence of close association between psychotherapeutic thinking and psychopathologic information. Not all physicians have therapeutic talent. It is essential that they do not have a defensive attitude toward bringing to light the patient's emotional difficulties.

R. W. Hall[8] believes that psychotherapy can be organized in two ways: (1) By the creation of a special psychotherapeutic department to be relieved of all administrative routine; and (2) by the development of a psychotherapeutic ability in promising personnel. At St. Elizabeth's, some 15 years ago, Dr. White innovated a special psychotherapeutic department. At the present time the hospital continues with this method and has three psychotherapists, all of whom are analysts, to deal with the treatable type of cases. Psychotherapeutic problems are presented along two main lines—adaptation and insight. The development of psychotherapeutic talent in promising personnel is the most practical plan. It is not difficult to pick out those who have ability to establish *rapport* and gain confidence and respect of their patients. The service possibilities of the junior physician should not be ignored, and those who have some psychotherapeutic ability should be given more time to deal with such problems. Although only a small proportion of mental hospital patients are suitable for intensive psychotherapy, many might be helped by occasional interviews. Much importance should be attached to the initial interview after the patient

is admitted to the hospital. His first impression is usually a lasting one and every effort should be made to make this favorable. The initial interview should orient the patient as to the circumstances and reasons for his hospitalization and should outline to him in a frank and systematic way what the hospital plans to do in his case, and what is expected of him. Of no less importance is the psychotherapeutic attention given just before discharge. At this time there should be a review of the patient's assets and a consideration of his past psychiatric experiences. We cannot disregard the importance of nurses and attendants in a psychotherapeutic organization.

At Stockbridge, H. K. Richardson[9] states that no one school is followed in their approach; however, it is principally a genetic dynamic developmental formulation of causal relationship and factors. It attempts to develop a permanent solution, understandable to the patient. When the patient enters Stockbridge, the history is obtained from him and his relatives; he is assigned to his hospital unit or "inn," and he is put on a regulated schedule of work, play, relaxation and rest. Daily interviews are held in which historical relationships as to his family life, his reaction to parents, dreams, preoccupations, or disturbances of childhood, adolescence, and adulthood, and evidences of maladjustment of the patient are gone into. The patient learns to "talk things out," and the doctor assumes the attitude of a sympathetic listener. If there is need, suggestions may be made or word association may be used to uncover material that is otherwise hidden. Reëducation proceeds on three levels: (1) Understanding of the problem and outlining a procedure to correct them by the patient; (2) application of this technique in the friendly limited environment of the hospital; and (3) an attempt to apply this same procedure away from the hospital and without the crutches upon which the patient has leaned. The therapy is further supplemented by five pamphlets: One furthers his information on levels of integration and gets him away from the mind-body conception; a second treats the possibility of somatic response to emotional difficulties; a third discusses maladaptation; a fourth deals with nature and function of his neurosis; and the last is a treatise on rest and relaxation as it may be applied.

Concerning psychotherapy in public mental hospitals, R. H. Hutchings[10] feels that the removal of the patient from his home to the institution is of first importance. Thus we separate him from the difficulties of the environment in which the psychosis developed and conditions which are likely to prolong it. Hospitalization gives him an opportunity to think of his conflicts as remote and takes him into an environment in which he can begin to reconstruct his past experiences and perhaps develop new emotional attitudes. The first impression the patient receives on entry is of paramount importance. The first contact that the prospective patient makes with the institution is in the person of the transfer nurse or attendant whose appearance and greeting, poise and tact are determinants in the impression to be gained by the patient. The receiving room or building should be inviting in appearance. The personality of the physician whom the patient meets in the reception room should be attractive. All these contacts with representatives of the hospital play important rôles in the establishment of *rapport*. The time to establish rapport, to gain good

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transference, is the time of making the formal mental examination. The importance of making this examination as soon as possible after admission and of keeping the patient practically isolated until it is done is emphasized. The value of frank talks with the physician cannot be too highly estimated. Patients who are at all communicative appreciate it and find relief in talking over their conflicts and problems. One's object is to induce the patient to alter his beliefs for himself; to argue with him is merely wasting time and may bring about a negative transference. The most important psychotherapeutic adjunct is occupational therapy. The instructor must be a good teacher and must be able to interest and stimulate the patient. Occupational therapy is designed to prepare the patient to enter into larger social activities outside of the institution; its aim is to reëstablish his lost capacity to coöperate harmoniously in group activities. Occupational therapy is one of the most effective means in aiding him to regain his community coöperation and teamwork. Recreation and amusements afford another therapeutic adjunct. Group activities bring out the introverted type of patient and are essential in socializing his interests.

In our own University Clinic,[11] we found that, in 1933, 60 of 116 psychiatric consultations asked for by the General Hospital were psychoneuroses, a total of 51%. It is conservatively estimated that one-third of the cases seen in the outpatient departments of this same institution present functional problems.

Our approach[12] to these problems and methods of psychotherapy in this clinic is somewhat as follows:

Any patient who comes is requested to describe as fully as possible the complaints that bring him to the clinic. These obtained, the history of their development determined, then this material is supplemented by a physical and mental examination.

The story, as given by the patient, is as objective as possible, based upon concrete experiences. The complaints are stated fully and recorded in the very terms of the patient. These facts are supplemented by those obtained from relations, friends and your own observation. There is a sincere search for the factors at work, the development of the condition, its working and effects and the modifiability of the whole. We attempt to get away from such complaints as "fear," "nervousness" and "depressed" and substitute for them concrete situations and reactions in order to keep on a ground of objectivity. It is important to use, wherever possible, the patient's own expressions and terminology and to stay away from complicated terms unintelligible and confusing to our patient.

Rapport is essential to good psychotherapy, but it must be a healthy, normal relationship and not one of supernormal type of suggestion and of so-called transference. It should be devoid of a relationship of anticipation, devotion and excessive personal dependence. It is much more acceptable to make it a rapport between physician and problem than physician and patient. It strives to have the patient use his resources whether the doctor is there or not.

It is necessary to attack the individual problems on an open talking basis with a goal of desensitization on the part of the patient to his difficulties. Repeated "rehashing" occurs until we feel that our client now discusses his problem without the emotional turmoil that brought

him to us. There must be, however, more than aëration and desensitization; there must be concrete and personal reëxperiencing of situations with a sensing of available opportunities for readjustments.

Part of each interview is given over to an account of the last 24 hours. Past experiences are reviewed to overcome disturbing sensitiveness and other obstacles. We talk in terms of life as it occurred and occurs and not in terms of word pictures of a fixed brand of theory. The case is formulated to the patient in terms he can handle, but first he is encouraged to size up the situation himself; this is more acceptable and lasting.

Another measure used is appeal through the more personal type of rapport; a third, persuasion; fourth, an intellectual-emotional winning over to an interest and participation in the day's routine and plan; the last, and most hoped for, the building up of a philosophy of understanding and of work and rest out of the patient's *own* associative material.

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F. G. E.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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MERCY HOSPITAL, PITTSBURGH, PA.

CONCERNING SOME RECENT CONTRIBUTIONS TO THE PHYSIOLOGY AND PHARMACOLOGY OF RHINOLOGY.

DURING the past year or so, oto-rhino-laryngology's kaleidoscope has been revolving with such bewildering rapidity that accurately to pick the prevailing pattern would require a master hand. Even so, it is clear that oto-rhino-laryngology's active phases have been chiefly in the domain of the experimental physiologist and pharmacologist, the allied branches of experimental biochemistry, biophysics and pharmacodynamics and applied experimental chemotherapeutics.

Accordingly, for the purposes of this review, have been chosen several recent contributions of seemingly basic significance and practical value not so much for their demonstration of fact as for their demonstration of method.

Under the title "Ventilation of the Nose and Accessory Sinuses: Oscillographic Method of Investigation," O'Malley[1] presents a preliminary communication concerning the physical and physiologic phenomena of air currents which occur in the nasal passages during the act of respiration. As olfaction in man has become of less importance, the respiratory rôle of the nose becomes the dominant function. The chief physical factors concerned in the ventilation movements of gases in Nature, and which appear to be present to some degree in the nose and sinuses, are listed as: (1) Perflation [expiration]; (2) aspiration [inspiratory]; (3) diffusion; (4) conduction; (5) radiation; (6) convection; (7) evaporation; and (8) expansion. In its present form, the oscillograph is registered on a revolving drum by a writing style attached to a tambour into whose air chamber a rubber tube, connected with the intranasal cannula conducts the air currents. For intrasinus determinations, the cannula is inserted after "proof puncture of the antrum or other accessible sinus." The mode of procedure consists of a complete detailed history and elicitation of the physical findings of the patient; transillumination, Roentgen ray and "proof puncture" of the sinuses, all of which is followed by oscillographic tracings before and after (depending on the results of) light, air and suction tests. These are described in the text and numerous oscillographic tracings, taken under numerous conditions, are presented. The author, from his observations, believes: (1) That the air in the accessory sinuses with patent ostia is in constant respiratory phase with that of the nose; (2) that their air pressure variations synchronize; (3) that air pressure variations can be shown in all parts of the nasal passages under all conditions of respiration; (4) that partial vacuum pressure in the sinuses can be demonstrated where no sinusitis exists; (5) that the same can be shown in acute and chronic sinusitis; and (6) that an influence of this mechanism in aggravating the inflammatory changes in both types of cases is indicated. Finally, the author promises to present further data on 20 other points, which he enumerates, the last of which is the "interdependence of ciliary action and air pressure variation currents."

In a comparative anatomic study, Eckert-Möbius[2] states that there are 3 main theories regarding the functions of the paranasal sinuses: (1) To lessen the weight of the skull and to provide certain adjustments needed in the facial skeleton, such as spacing of teeth, etc.; (2) to increase olfactory acuity, especially by sniffing; and (3) to warm and moisten the inspired air. Of these, the author recognizes only the third as being important. He considers the following evidence: (1) The accessory nasal sinuses which, beginning as outgrowths of the mucosa of the upper respiratory tract, like the nose, are lined by columnar ciliated epithelium containing goblet cells; (2) in the large and fleet mammals with an active respiratory apparatus (elephant, giraffe, buffalo), the paranasal sinuses are well developed, whereas slower moving animals, particularly those living in a watery environment (hippopotamus, walrus) whose inspired air does not need moisten-

ing, have no, or only rudimentary, sinuses; and (3) the highly pneumatized skull of the land-loving brown bear is contrasted with the virtually non-sinus-containing skull of the aquatic polar bear.

While in experiments the use of ciliated epithelium from amphibians and other lower forms may often be expedient and sometimes unavoidable, Proetz[3] points out that deductions made from the results obtained may not properly be applied to human membranes. Recalling that air-breathing animals are required to supply their own fluids to keep the nasal cilia beating, while the water inhabitants are not, the author insists upon the use of mammalian membranes for experimental purposes. Accordingly, and so as to approach normal conditions as nearly as possible, parallel studies of extirpated human nasal mucosa and the nasal mucosæ of rabbits *in situ* were made, both under direct vertical vision with a magnification of 104 diameters and a motion picture record to permit repeated examination and deliberate analysis. The methods and apparatus employed in these ingenious experiments —designed primarily to determine those conditions which permit, pervert or destroy the maximum efficiency of the ciliary function—are fully described and illustrated. With one exception, 22 specimens removed at operation from diseased human sinuses showed the cilia to be quite normal in appearance. The time required for a single cycle of motion in both rabbit and man varied from $\frac{1}{4}$ to $\frac{1}{10}$ sec. The direction of wave propagation is, or can be, in the opposite direction to that of the effective ciliary stroke. From the clinical standpoint, the most important observation is the effect of drying, which caused a cessation of ciliary activity. If allowed to continue for 15 to 18 min. the ciliary motility could not be restored by moistening. Although the results on the *in vitro* human experiments and the *in vivo* rabbit investigations presented no gross differences, "it is not intended even to suggest that they (*i. e.*, differences) do not exist until a very large amount of material shall have been seen, and until the errors possible to the rabbit experiment have been reduced as far as humanly possible."

In a "Comparison of Ciliary Activity Under *in Vitro* and *in Vivo* Conditions," Lucas,[4] having previously emphasized[5] the need for methods permitting direct observation of ciliary activity, describes such a method whereby cilia arranged in a field, as they are in the pharynx of the frog and the nasal cavity and sinuses of higher animals, may be kept under direct observation. Virtually the same ciliary responses were obtained *in vivo* and *in vitro*. Minor differences between ciliary behavior and mucous flow *in vivo* and *in vitro* may be attributed perhaps to the absence of blood circulation in the latter condition. Lucas' results have demonstrated that the cilia of the frog's pharynx in the absence of extraneous factors maintain an inactive quiescent state, and that with mechanical stimulation from any source the cilia are stimulated to activity which ceases when the cause is removed. Therefore, he says, the base line for physiologic studies of ciliary behavior *in vivo* and even *in vitro* is *zero* for the frog's pharynx.

In a later contribution, Lucas[6] gives minutiæ of his method for direct observation of cilia *in situ* and illustrates his apparatus. From the evidence thus far available in the experiments on invertebrates, amphibians and mammals, he presents the following opinions: Ciliated cells do not immediately adjust themselves to new conditions

imposed by injuries to adjacent epithelium; after reversal and reimplantation of ciliated tissue in the same site, the original polarity of implanted and contiguous tissue is maintained; regenerated ciliated epithelium will have the same polarity as it originally held in relation to the tissue from which it originated if the internal and external factors are unchanged.

Quite recently, Lucas and Douglas[7] employed the same method along with the well-known methods of applying carbon particles to the mucous surfaces of the noses of various kinds of mammals, in order to learn the significance of the direction of mucous flow in various regions of the nose and its possible relation to physiologic and anatomic factors. In all the animals used—mouse, rat, rabbit, oppossum, cat, sheep and cow—the direction of the mucous flow was toward the anterior nares, and the region of greatest ciliary activity was in the upper part of the nose, all of which is exactly opposite to the condition found in man and monkey. Furthermore, it was learned that the direction of air currents for cats was equally different from those marked out for man. Therefore, it was concluded that the direction of air currents through the mammalian nose is a factor in the development of the pattern of mucous flow and that the two are inversely correlated.

Several noteworthy contributions concerning the immediate direct effect of the various drugs used daily in the nose on the speed and continuation of ciliary activity have appeared recently.

Badertscher[8] used microscopic observation of the duration of the ciliary motion of the frog's pharyngeal epithelium as an indication of progressive injury to mucous membranes. The ciliary motion of infusorial cells (paramecia) was studied for comparison. It was found that the preparations employed were "rather markedly toxic." With the exception of methylene blue, the paramecia were more susceptible than the pharyngeal epithelium, the ratio being from 2 to 8 for phenol, meroxyl and eosin; from 16 to 40 for acriflavin, pyridium, mercurochrome and gentian violet; 375 to 500 for hexylresorcinol and iodin; and infinite for quinin.

In an attempt to determine why such beneficial results follow the local applications of silver nitrate in vasomotor rhinitis, Lillie and Childrey[9] performed a series of experiments on rabbits, 20% solution of silver nitrate being applied to the nasal mucosa. At varying intervals afterward, the animals were killed, and sections of the nasal mucous membrane, which had been treated, were studied histologically. Following this procedure, the epithelium begins to regenerate as early as 1 week after treatment, and cilia may appear 3 months afterward. This epithelium does not appear normal, but is pseudostratified and contains an abnormal number of goblet cells. The underlying tissue is fibrous and thick, and, although it contains glands which have apparently regenerated, it is abnormal in appearance and markedly infiltrated with cells. Perhaps of greater importance in the study of vasomotor rhinitis is the fact that the nerve fibers show cellular infiltration and vacuolization. These changes in the nerve fibers may explain the beneficial results obtained in the treatment of vasomotor rhinitis by the topical application of silver nitrate solution to the membranes in the region of the nasal ganglion.

Lierle and Moore[10] studied the effects of various drugs on the activity of the unprotected cilia of the upper respiratory tract of man, the dog and the guinea pig: (1) A small series of determinations was made of the effects of certain drugs on the ciliary activity of strips of tissue mounted in a special microscope chamber; (2) 20 determinations were made of the effects of a larger number of drugs on the ciliary activity of the unbroken mucosa of the turbinates of freshly killed guinea pigs *in situ*. It was learned that: (1) Tap and distilled water when applied to the upper respiratory tract cause slowing of the ciliary beat; (2) 3% ephedrin hydrochlorid is not detrimental to ciliary activity but at times increases it slightly; (3) 5% cocain hydrochlorid is not detrimental to ciliary activity, but 10 and 20% solutions produce definite slowing, with good recovery; (4) mild silver protein in concentrations of 5, 10 and 20% produces an initial speeding of ciliary activity. This is followed by a slowing, which may be due to the water solvent rather than to the drug; (5) 0.5% eucalyptol has no deleterious effect on ciliary activity; (6) 0.5% menthol and, to a greater degree, 1% menthol have a mildly depressing effect on ciliary activity; (7) 1% thymol, 0.5% thymol and 1% eucalyptol, in the order named, are definitely detrimental to ciliary activity; (8) a 1 to 1000 solution of epinephrin hydrochlorid, 2% zinc sulphate and 2% mercurochrome, in the order named, are definitely detrimental to ciliary activity; (9) 0.5% silver nitrate is immediately and fatally detrimental to ciliary activity. In no instance was it possible to start the cilia beating again after its application.

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PHYSIOLOGY

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Experiments on Chemotropism of Leukocytes. MORTON MCCUTCHEON and H. M. DIXON (Laboratory of Pathology, University of Pennsylvania). The chemotropic response of human polymorphonuclear leukocytes to different types of microörganisms was evaluated through experiments *in vitro*. Under the microscope the net distance was

measured by which each cell approached a clump of bacteria, and this distance was divided by the total length of the path of the cell. The resulting ratio is a measure of the chemotropic response, having as extreme values +1.00 if the cell moves directly toward the bacteria, −1.00 if the cell moves directly away from them. With staphylococci, streptococci, pneumococci, typhoid and tubercle bacilli, Micrococcus tetragenus and certain yeasts, mean ratios ranged only from +0.73 to +0.86, indicating approximately equal attraction under these conditions. With the yeast, Torula histolytica, the ratio was +0.57. Control leukocytes, wandering in fields free from known chemotropic influence, gave a value of +0.07. With substances other than bacteria a wide range of values was obtained: gelatin, 0.00; dried blood, +0.18; dried leukocytes, +0.25; starch paste, +0.71.

The Present Status of the Coagulation Problem. An Experimental Review. HARRY EAGLE (Laboratory of Bacteriology, University of Pennsylvania). The amount of thrombin formed in a mixture of plasma, platelets, Ca and fibrinogen is independent of the fibrinogen, and varies directly with the amount of the plasma factor (prothrombin). Platelets and cephalin accelerate thrombin production, but do not affect the total quantity formed. Treatment of horse thrombin with Na-oxalate does not affect its activity, although the Ca is precipitated quantitatively. This does not exclude the possibility that thrombin is a Ca-compound present in minute molecular concentration, but it does confirm the view of Hammarsten that Ca cannot be an intrinsic part of the fibrin molecule.

There is no simple linear relation between thrombin and fibrin. The quantitative relationships between the two and the rate of thrombin disappearance suggest that thrombin is an enzyme, as originally believed by Schmidt, rather than a stoichiometric component of the fibrin molecule. There is no significant change in the pH of the solution during the coagulation of fibrinogen by thrombin.

None of the four theories as to the reason for the fluidity of circulating blood (heparin, pro-prothrombin, platelet-stability, antithrombin) adequately explains the phenomenon. Heparin does not act by combining with prothrombin, but by retarding its transformation to thrombin. Platelets *in vitro* remain sufficiently intact in the presence of Ca to be readily centrifuged; and the sediment is quantitatively as active as the original platelet suspension. Thrombin injected intravenously in quantities less than that which would be liberated from the blood suffices to cause intravascular coagulation and death.

The retarded coagulation of hemophilic blood is not a platelet deficiency. Normal and hemophilic platelets accelerate thrombin production and coagulation to exactly the same degree. As originally believed by Addis, the deficiency lies in the prothrombin. Although present in normal concentration, it is transformed to thrombin by platelets and Ca more slowly than normal prothrombin.

Studies Concerning the Nutritional Value of Slightly Rancid Fat. DOROTHY V. WHIPPLE (Department of Pediatrics, University of Pennsylvania). The chemical condition of the fat of a ration has been found

to be an important factor in determining the nutritional value of the ration.

Three comparable groups of rats were fed a fat-free basal diet adequate in all known dietary essentials. One group was given, in addition to the basal ration, 0.1 cc. daily of fresh neutral fat, the second group received 0.1 cc. daily of slightly rancid fat (peroxid value 15 to 20 millimols per kilo), and the third group was kept without any fat. The animals receiving the good fat grew normally and remained in apparently good health for the duration of the experiment (288 days). The animals in the fat-free group grew at a slower rate for the first $5\frac{1}{2}$ months, then began to lose weight and finally died with symptoms of the fat deficiency disease described by Burr and Burr. The rats receiving the oxidized fat grew at about the same rate as the fat-free controls, and developed symptoms very similar to those of the fat deficiency disease in the same time period; their length of life, however, was longer than the fat-free animals.

A curative experiment was done in which comparable trios of animals suffering from severe fat deficiency disease were fed: (1) neutral fat; (2) partly oxidized fat; (3) no fat.

The animals receiving neutral fat were cured of the disease, those receiving no fat died, while those receiving oxidized fat died more quickly than the fat-free controls.

It is tentatively concluded that partly oxidized fat is unable to replace neutral fat in the diet, possibly due to the destruction of the double bonds in the nutritionally essential fatty acids; and that there may be a toxic factor produced in the fat by the oxidative process.

Studies on the Living Kidney Glomeruli of the Frog. G. S. DE RENYI (Laboratory of Anatomy, University of Pennsylvania). Freshly isolated and fixed and stained preparations of the glomeruli of frog kidneys were examined microscopically. The following conclusions seem justified:

A. The small vessels in the glomerular tufts are true capillaries. Typical adventitial cells are attached to their outer surfaces. In a fresh condition these cells do not exhibit the property of contractility when stimulated mechanically.

B. The endothelium of the capillary loops differs in some respects from that in other capillaries.

C. The outer surface of the loops possesses no epithelial sheaths.

D. A gelatinous, highly viscid, optically homogeneous tissue covers the loops. This substance possesses a certain degree of elasticity, and contains cellular elements. In its physical properties it resembles the homogeneous matrix of connective tissue. It adheres to the walls of the loops and to their adventitial cells.

E. Since there is no epithelium upon the outer surface of the loops, epithelium plays no rôle in the filtration of urine. Only three structures are involved in the mechanism of urine formation: endothelium, a thin membrane, and a highly viscid, gelatinous tissue.

A Gonad-stimulating Extract from Alfalfa. MAURICE H. FRIEDMAN and GERTRUDE S. FRIEDMAN (Laboratory of Physiology, University of Pennsylvania). For a variety of reasons it was thought very prob-

able that the pituitary gland did not elaborate its hormone from simple, widely distributed chemical substances, but required from the environment rather complex precursors (or active materials similar to the hormone) which were rather limited in distribution. If this were true, it was thought that the green plant would afford a likely source of such materials. Consequently alfalfa was subjected to a cold alkalin extraction and the resulting filtrate treated according to the Katzman-Doisy benzoic acid method for the extraction of the activity of pregnancy urine. The extracts so produced proved to be capable of stimulating the ovaries of the isolated rabbit, so that it can be said that alfalfa is capable of yielding a gonad-stimulating substance. Whether or not this fact has any direct physiological significance remains to be seen.

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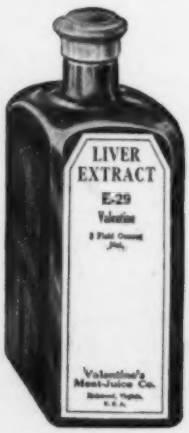

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Of further interest is the paper by Ruffin and Smith entitled, "The Treatment of Pellagra with Certain Preparations of Liver" in the April, 1934, issue of *This Journal*.

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